ROYAL COMMISSION ON MATTERS OF HEALTH AND SAFETY

ARISING FROM THE USE OF ASBESTOS IN ONTARIO

CHAIRMAN: J. STEFAN DUPRE, Ph.D.

COMMISSIONERS: J. FRASER MUSTARD, M.D.

ROBERT UFFEN, Ph.D., P.ENG., F.R.S.C.

COUNSEL: JOHN I. LASKIN, LL.B.

APPEARANCES: P. Casgrain, Quebec Asbestos Mining Association

L. Jolley, Ontario Federation of Labour

J. McNamee, Government of Ontario

T. Lederer, Government of Ontario

180 Dundas Street
Toronto, Ontario
Friday,
January 15, 1982

VOLUME XXXIV

ROYAL COMMISSION ON MATTERS OF HEALTH AND SAFETY

ARISING FROM THE USE OF ASBESTOS IN ONTARIO

INDEX OF WITNESSES:

180 Dundas Street
Toronto, Ontario
Friday,
January 15, 1982
VOLUME XXXIV

180 Dundas Street
Toronto, Ontario
Friday,
January 15, 1982
Volume XXXIV

THE FURTHER PROCEEDINGS IN THIS INQUIRY RESUMED PURSUANT TO ADJOURNMENT

APPEARANCES AS HERETOFORE NOTED

MR. McNAMEE: Mr. Commissioner, being as it's a New Year, it's probably time to ring out the old and ring in the new, and we have a new ball player for the government. He is going to carry the torch from now on, a very capable lawyer. His name is Tom Lederer, sitting to my right.

Tom is a graduate of U of T and Osgoode Law School. He has spent several years with the Civil Litigation Branch of the Attorney General's Department, and is presently, the last few months, being working with Osler Hoskin.

I have already briefed him on the....basically on the background, and I've indicated, and I wish to put it on record, that I certainly have been very pleased to have the opportunity of spending the last year with the Commission. It's a very capable, well-run Commission and competent people run it.

I am looking forward to, I think, a very sterling report that will probably throw very strong new insights into this perplexing problem that we have been dealing with.

Maybe if I just introduce Tom so he'll know. Reading from left to right, Dr. Uffen, Dr. Dupre and Dr. Mustard.

MR. McNAMEE: (cont'd.) I have already given his qualifications, but I would like to welcome him and at the same time I want to say thanks to Mr. John Laskin and his capable staff for the excellent preparation of all the witnesses, his helpfulness.

I don't think this Commission could run without Linda Kahn. I think it would grind to a halt. She and her capable assistants have certainly made it much easier for everybody to digest the great mass of technical evidence that gives pause to lawyers as well as the Commission. I wish to thank you again.

I'm not signing off until the end of Dr. Davis's evidence. That's probably a good time when there's not so many witnesses. I'm sure that Tom is looking forward to it and I'm sure you will be as happy as I was to have spent the year with you.

MR. LEDERER: Thank you.

DR. DUPRE: Thank you, counsel.

Welcome to the proceedings of this Commission, Mr. Lederer, and may I say that you have not only a distinguished but very learned predecessor in Mr. McNamee. Learned, as they say, not only in the law, but by now, thanks to the summer school through which he slaved with all of us, learned in many, many aspects of the health effects of asbestos.

On behalf of my colleagues, Mr. McNamee, I can assure you that we have warmly welcomed your presence with us and we regret your departure.

MR. McNAMEE: Well, I would like to get a copy of the report.

DR. DUPRE: So would we.

Well, we do indeed welcome a New Year and it is, of course, a year in which my colleagues and I are firmly resolved is, of course, the final year of this Commission.

At this juncture may I ask Mr. Laskin, are there any other points that you or your colleagues wish to raise

DR. DUPRE: (cont'd.) before I greet our witness?

MR. LASKIN: The only point I have, Mr. Chairman, other than welcoming Tom Lederer as well, is to tell you regrettably our friends from Washington, Mr. Warren and Mr. Hardy, will not be with us today and they send their regrets.

I have no other preliminary matters. I don't know whether my friends behind me do or not.

DR. DUPRE: Miss Jolley, or M. Casgrain?

M. CASGRAIN: I think for the record I think I would like to take note of the fact that the Commission was good enough to attend at Thetford and at Asbestos to visit the installations of some of the mines, and to tell you that the operators were delighted to have the Commission attend at their mines and they do, of course, hope that you will find occasion to return to perhaps a more detailed visit.

That's what they say, but of course you know a mining operator will always tell you that you will never see the end of the hole they are driving, so if you were to agree with them you would be there all the time.

Nevertheless, they want to thank you for having come to Thetford and Asbestos.

DR. DUPRE: That is most gracious of you, M. Casgrain. I certainly would want to say for the record that we were most pleased with all of the arrangements that were made by your Association for us that enabled us to cover three different sites in what was approximately fourteen hours of three-stop motoring across the landscape.

Now, ladies and gentlemen, it gives me great pleasure on behalf of the Commission to greet our most distinguished witness, Dr. John Davis, of the Institute of Occupational Medicine in Edinburgh.

Dr. Davis, I can assure you, sir, your reputation

DR. DUPRE: (cont'd.) preceeds you. We thank you most warmly for having put yourself to the inconvenience of displacing yourself over such a great distance, and may I now please invite counsel to guide you in the instruction that you will be giving us today.

MR. LASKIN: Thank you, Mr. Chairman.

Could I ask Miss Kahn to have the witness sworn?

JOHN MICHAEL GORDON DAVIS, SWORN

EXAMINATION-IN-CHIEF BY MR. LASKIN

Q. Dr. Davis, for the purpose of our record, you have in front of you two volumes which contain a selection of your publications, and for our record we have given those two volumes an exhibit number and it's exhibit forty-seven.

In the event that we refer to any particular article of yours, we will likely refer to it by tab number within exhibit forty-seven.

Could you or would you be good enough just to state very briefly for the benefit of all of us your educational background and where you have been since you left university, where you are presently and what your position is?

A. Yes. I was a student at the University of Cambridge, rather an unusual one in that I went to Cambridge as a medical student but having been there a little while I decided I didn't want to undertake clinical practice, I wanted to do research entirely, so I changed from a full medical course to take the subject of pathology as an academic subject, and then went on to take a Ph.D. in pathology rather than undertake clinical medicine.

Having done that, I became an Assistant Director of Research in the Department of Pathology at Cambridge, where I started to work on the subject of asbestos bio-effects, and I was

A. (cont'd.) there for eleven years, from 1960 to 1971, when I moved to the Institute of Occupational Medicine in Edinburgh as head of the pathology branch there, which in fact we set up at that time.

There we have continued to undertake work on asbestos problems, but in fact have expanded interests into other fields like early effects of coal and other industrial hazards.

Is that an adequate summary?

Q. That's most adequate. Thank you, Dr. Davis.

Can we begin by you telling us something about which we have heard little or nothing during our expert testimony this past summer, and that is some explanation as to what happens to asbestos fibers when they get inside the human body, when they get in cells or in tissue, and perhaps we can then get into some discussion of the process of the disease as it relates to asbestos.

A. Certainly.

Can I start by illustrating a few points on the blackboard?

Q. By all means.

A. Then I have some slides loaded, which I think will help. As you might expect, they are slides of some pictures that have appeared in publications so maybe they will be recognized.

Now, if I am talking at the blackboard can I be heard properly?

Q. If you take the microphone with you.

A. Can I first apologize if I make things too simple for anybody, but perhaps it would help if I start really right at the beginning when it comes to cells and asbestos.

First, very simply indeed, can I perhaps set the scene of the sort of sizes we are talking about. Here I am starting to draw a very simple diagram of a cell, which has

THE WITNESS: (cont'd.) two components central around the nucleus, which is in fact simply genetic material, surrounded by an area we call cytoplasm, which is really a biochemical factory where all the activity occurs.

The purpose of the nucleus is simply to provide the blueprints for the factory, information needed funnels into the cytoplasm where it is activated.

Now, if we assume that that cell is one of the phagocytic cells of the body, or macrophages - these are scavenger cells that were designed initially to clear up foreign debris in tissues, foreign material that could find its way into tissues. Naturally in the course of evolution the main reason for this sort of defence system was to deal with biological entities like foreign bacteria, but since man has started to insult himself with other things, like asbestos, the body system has done its best to cope.

Now, the phagocytic cells, or macrophages, in size something...well, now round it out, let's say about twenty microns...and that's a size of some importance. A resting macrophage might look something like that, but when they become actively phagocytic, that's when they start hunting for foreign material to engulf, the surface membrane becomes modified and produces a lot of leaf-like processes. In fact, the cells can be looked upon as a multipored octopus.

The purpose of these extended membrane processes is obviously to act as feelers to actually find the foreign material, whether it's bacteria or asbestos.

Once foreign material has been found by an appropriate process...and let's draw a short asbestos fiber there as the example...first this tends to fold back onto the cell membrane. These things are not so much fingers as leaf-like extensions, so that if they fold back they can press foreign

THE WITNESS: (cont'd.) material against the surface of the cell. I have a picture of one of them doing it here. You see foreign material inside.

When this happens, the membrane fuses again at that point and you merely have the foreign material enclosed in a vesicle which, a little later on, tends to get moved inside the cell itself, with its enclosed material.

I thought perhaps it was useful to draw that out since the slides that I'm showing have not got magnification lines on them.

Now, is that clear enough or would it help to lower the lighting? Is that all right?

Most of the slides in this series are electron microscope pictures obtained of tissues which have been experimentally treated with asbestos fibers. In fact, for technical reasons all this experimental work has been done with chrysotile.

The technical reason is simply that in order to prepare specimens for the electron microscope we have to cut exceedingly thin sections of the cells, and chrysotile is soft enough to cut as we would like. The amphiboles are too tough. It was exceedingly difficult to get electron microscope pictures containing the amphiboles.

So this first slide really demonstrates the points I have made on the blackboard. That is a section of the cytoplasm of a macrophage. There is no nucleus actually in a plain section. So imagine the section running across something like that, and you can see a number of the vesicles I told you about and also, on the surface of the cell, you can see quite a number of these elongated processes. You can see the fat cell has already engulfed quite a number of small chrysotile fibers.

DR. UFFEN: Do they ever get into the nucleus?

THE WITNESS: Exceedingly rarely. I'm not sure that I have ever found a single example where I have seen fiber actually in a nucleus. I don't know that anybody else has produced a convincing picture.

It may be that with some fibers if the area is damaged that cell could almost spike its nucleus on a fiber, but I'm sure that would be a lethal happening, and maybe that's why we don't find it. I simply have seen no example of it.

The next few slides simply illustrate these phagocytic vesicles at high magnification. The magnification here is probably something in the order of forty or fifty thousand times, and that bundle of chrysotile crystals would be something between two and four microns in length.

One of the things that you will notice there, and it is a matter of some importance relating to what I have to say later, is that you will notice how the bundle chrysotile...and you'll know well from the previous discussions on asbestos...is made up of quite large numbers of individual fibrils, each of which have a very small diameter - something in the order of three hundred, four hundred angstroms, I guess. So one quite small fiber can contain quite a large number of subunits, and that is clearly visible on that section.

That's another example of chrysotile fibers enclosed within one of these phagocytic vesicles. At the bottom of the photograph you can see where one of these finger-like processes is folded back onto the cell surface.

Perhaps you won't mind if I buzz backwards and forwards to point to things.

Here you have some of these finger-like processes on the surface of the cell, and here is where the process has folded back to form a vesicle. It looks as though in that case it failed to bring any asbestos with it. Inside this vesicle

THE WITNESS: (cont'd.) are quite a large number of chrysotile crystals. In this case the crystals have separated and you are dealing with the individual subunits of chrysotile. That's quite a long one, perhaps one and a half microns to two microns on its own.

Now, having reached this vesicle stage, two things seem to be possible. One is that extraneous material is added to the vesicle and it becomes solidified into one of these rather dense structures which you can see is still surrounded by a membrane on the outside...a membrane on the outside and individual chrysotile crystals in the middle.

We're still at the level of a forty/fifty thousand magnification.

Now, the material added to these structures is of some importance because it relates to the normal biological function of this phagocytic process. If the foreign material had been a bacteria, it would consist of normal biological chemistry - proteins, lipids - and would be easily digested and the scavenger cells, the macrophages, having got the foreign material into a bag, secrete into the bag special chemicals, enzymes, which are capable of breaking down biological substances, and this is how bacteria are killed.

When the cell has phagocytozed asbestos, it simply has to go through the same routine because that's the only routine it knows. So that the dense material surrounding the asbestos fibers now will certainly contain enzymes capable of breaking down the cell structure.

In many instances I'm sure everything remains in those little bags, which probably become inert and last as long as the cell does, and perhaps cause no further problem at all.

But there does seem to be an alternative for this process, which you can see there. It is possible for the asbestos

THE WITNESS: (cont'd.) fibers to break their way out or puncture their way out of the vacuum, the vesicles. You can see here is basically the vesicle with the membrane around most of the surface. Here, some chrysotile crystals that have obviously punctured the bag at this point are in the process of getting out.

Now, it may be that when this happens any of the enzymes liberated around the fiber in the first place, escaping into the cell, can actually kill the cell.

I think it certainly happens in some cases, and when this occurs after a period of time the cell breaks down completely and the asbestos it contains is liberated, and the whole process starts over again. Most of the fiber is actually removed from the tissues completely, which it can be from lung tissue and I shall discuss this in a minute. It simply continues to attract scavenger cells to engulf it, hopefully to immobilize it. As long as the fiber remains, this process will continue.

MR. LASKIN: Q. Do I take it that the enzymes don't have any effect in breaking down the fiber itself in the same way that the enzymes break down bacteria within a cell?

THE WITNESS: A. As far as we know, they have no effect at all. They are designed to chop up specific chemical groupings which exist in the biological materials and which don't exist on the asbestos fiber, the asbestos surface, at all.

Q. So that if I understand it, while the macrophage has totally engulfed an asbestos fiber it's relatively immobile and presumably not...

A. The fiber is relatively immobile.

Q. And presumably not harmful. But if it's free, something...

A. I believe that to be the case. It's very difficult to prove. I believe that to be the case.

One point...I must point out that these phagocytic

A. (cont'd.) cells are naturally mobile cells. They have to be able to move about and to find the foreign material.

It's logical to assume that at some point...these are very greedy cells and I'll show some pictures later indicating that they can take up many, many particles of asbestos...at some point I can well imagine the stage is reached where they are so full they cannot move and have immobilized themselves.

Whether this is of importance in disease development we are not certain.

This is a photograph of a macrophage at slightly lower magnification - probably about twenty thousand. I'm sorry it's a little dark, but you can see that this cell has taken up quite a large amount of asbestos. On the outside here are two quite long fibers that have not been taken up by this cell, but since the stage at which this preparation was made was some months after asbestos treatment, it is logical to assume that these fibers were originally taken up by cells which died and this is the recycling process at work, and this cell is probably going to be involved in phagocytozing, engulfing, those particular fibers.

This is just another example of roughly the same thing - a cell being really greedy and taking up a lot of asbestos fibers. But all very short fibers, you will notice - something in the region of one, two or three microns in length.

Now, I'm not sure of the importance of this slide. One of the things that you will be interested in, of course, is how the fibers produce disease - that is to say, produce either scar tissue or fibrosis, or later on we'll probably be talking about tumor production.

The macrophages themselves are basically scavenger cells. They pick up fiber, foreign material. If they can't digest it, they try and move it, certainly, out of the way.

Now scar tissue or collagen is produced by a specific and a different cell type called a fibroblast.

THE WITNESS: (cont'd.) So how does the asbestos activate this type of cell?

This slide indicates that certainly some of the fiber-producing cells do actually engulf asbestos in their own right.

This is a fibroblast. Again, a small section of the cell, only part of the cell, the cytoplasm. On the outside of the cell here you can see the individual fibers of collagen, which is the material that scars are made of. This cytoplasmic structure happens to indicate a cell actively producing proteinaceous material of some type, and we can be sure in this case it's producing collagen.

Inside are a few crystals of chrysotile asbestos.

Now, a long time ago I think I made the suggestion that perhaps some of the phagocytic cells, or macrophages, actually changed into the fibroblasts, or collagen-producing cells. I'm not sure if that is correct. It may well be that some of the fibroblasts in the cells have only a small amount of phagocytic potential - they can take up some dust.

So we have the interesting possibility - is it the dust, the small amount of dust taken up by the collagen-producing cells that causes the scar tissue, or is it the dust actually inside the macrophages.

Now, you may have heard of the work of Professor Heppelston in Britain, who used silica dust...in fact, quartz dust... and showed that macrophages that have taken up quartz dust actually produced chemicals that were liberated from these cells and switched on the scar tissue cells and stimulated them to greater activity.

So there are these two possible pathways, and I'm sorry, I have no information on exactly how important each of them happens to be in the production of asbestos scarring.

Now, so far, the fibers I have shown you have been

THE WITNESS: (cont'd.) very small ones. This photograph is a very much lower magnification, probably five or six, seven thousand of the original photographs, and begins to deal with the subject of what happens to larger fibers that can get into lung tissue.

What you have here, basically, is a number of cells. At this point you can see for the first time the general outline I drew there with the nucleus of the cell in the middle. That's the genetic material, the blueprint factory itself. Surrounding it, the biochemical factory or cytoplasm. That's one cell, and another up there, and another there although the nucleus isn't included, another there and so on. Maybe a dozen in this picture.

These are macrophages. They are actually taking up chrysotile asbestos, and for the most part you can see you are dealing with small particles of the type I was showing previously.

Now, in addition, you have one really big fiber. This one is something in the order of thirty microns in length.

Well, this just happens to be too big for one cell to deal with and the body has developed a technique of walling up these large fibers, which I will try and demonstrate, and this is the first stage. A fiber is surrounded by cells, all of them actively engaged in taking up asbestos particles if they are small enough.

Once again I would attempt to illustrate the point that this bundle is made up of many, many subunits so that one big fiber potentially can produce a lot of little ones.

Now, the body does rather more than simply surround the big fiber with a lot of cells. It actually causes the cells to fuse, to produce super-big cells. In fact, they are called giant cells, which are big enough to deal with a large fiber. Because they are fused from a number of individual cells, they actually have a number of nuclei. They are not anucleate cells, but most cells

THE WITNESS: (cont'd.) have only one nucleus.

Now the process is rather interesting. We have talked about the formation of these leaf-like processes on the surface of the macrophages, and when a number of these macrophages, all actively trying to engulf material, surround a big fiber, they tend, I think, to almost try and phagocytoze, engulf each other and the surface processes get tangled up.

You can see that in this photograph. This is again a magnification of about sixty thousand times. In cross-section of these finger-like processes you can see that there is an end there to that process in that one, so that process belongs, we can trace it back, I think, to this upper cell.

Now, if we look there, there is an end to that process and you can trace it to the lower cell. So that these processes are intermingled. The cell is almost tying itself to another cell.

And then what happens in a way we certainly don't understand is that the membranes between these processes begin to break down into a series of vesicles, and when this is completed the vesicles tend to float away and the two cells have completely fused.

So that a large fiber can actually be engulfed by a whole series of cells which unite.

Now, so far we have talked about asbestos fibers simply on their own. There is one way the body reacts to them, the importance of which we don't entirely understand, and that is by a formation of asbestos bodies. Since the process happens around all mineral fibers, they tended to produce the general term 'ferruginous bodies'...ferruginous because the coating material certainly contains some form of iron.

Now, this photograph, again moder magnification, twenty or thirty thousand times, once more you can see you have a

THE WITNESS: (cont'd.) large bundle of chrysotile crystals...forty, fifty, a hundred small ones.

Now, surrounding the fiber is a thick layer of dense granules. These granules are ferritin material, which is an iron-containing protein that is normally found in tissues, and consequently the ferruginous body. It contains iron and we can recognize it by using a stain for colloidal iron which produces a blue coloration in the tissues.

Now, we certainly know that a very small percentage of all fibers become coated to form ferruginous bodies. Why do most of them fail to become coated? I'm not sure, but we do know something about the formation of the bodies and it may be simply a matter of the fibers ending up in the right position.

What seems to be necessary is for the fiber to be held in a position where the giant cells we have just talked about have begun to form around it but haven't completely fused themselves, so that the fiber is held in sort of a little local environment without actually being right inside a cell.

These next slides illustrate this process. Here we have a transverse section of quite a large bundle of chrysotile fibers. Then you can see these individual subunits - lots and lots of them. That membrane there corresponds to one of the vesicles surrounding a cell, but in most cases where body formation is occurring you can see that there is an outlet to the exterior.

Perhaps it doesn't show up too well on this slide. It will on the next one.

This slide shows that the first layer of foreign material put down around a fiber is rather light-colored granular material, which by chemical staining we can show to be mucopolysaccharide.

Then the iron-containing protein granules seem to be deposited on the mucopolysaccharide. Again, asbestos, now it's a much denser granule that is being produced. The important

THE WITNESS: (cont'd.) thing here is that there is a space there. If you follow it, it's like finding your way out of a maze, but eventually you can get to the outside of the cell.

Here are these leaf-like processes in the early stages that will lead to fusion, but they haven't yet fused. You can trace your way from the environment where the fiber exists to the outside of the cell at this point.

DR. UFFEN: Do you mind a question here?

I'm not certain I understand the explanation as to how the iron comes from outside and not from the irritant, from the fiber or dust.

THE WITNESS: Well, most types of asbestos, of course, don't contain iron. Amosite contains quite a reasonable amount of iron. Was this your question?

DR. UFFEN: No. I understand that the iron comes in from outside to make the ferruginous bodies. I want to make sure I understand it clearly, that it doesn't come from the irritant...

THE WITNESS: From the fiber itself.

DR. UFFEN: ...from the fiber, if there's iron in the fiber. I believe that's true, but I want to...

THE WITNESS: That is true. I think we can be sure of this, because the iron in the fiber would be chemically strongly bound. If it was removed, it would be removed in molecular form...as individual molecules.

Now, the coating of the ferruginous bodies can be shown to be these dense granules. Now, under very good electron microscope conditions, very thin sections, exceedingly high magnification, you can actually show that each granule has the structure of ferritin.

DR. UFFEN: Ferritin?

THE WITNESS: Ferritin, with four protein subunits with iron colloidals interlaced. I think this is accepted. I am

THE WITNESS: (cont'd.) not enough of a molecular biologist to go too much further, I'm afraid.

DR. UFFEN: Could I ask another question? Is there any sort of biological reason why those particular iron atoms would get into these little granules? They come from somewhere, the blood or...I guess.

THE WITNESS: Well, ferritin is the normal iron-containing protein in the body. That...and hemosiderin is a very similar one. In fact you can't be sure whether we are looking at is ferritin or hemosiderin. Hemosiderin is a breakdown product of the blood cells. Eventually it is handled by the liver and turned into bile pigments and excreted.

But the red cells, of course, the oxygen-seeking molecule in the red cells, hemoglobin, contains iron. It's essential for its activity that it contains iron, and when these red cells are broken down, the breakdown process involves adding the iron to the breakdown products...or rather the breakdown products continue to contain the iron. This material at some stage - it's hemosiderin - and exists as little granules or granule groups of molecules. So that this material is present in normal tissue, and some of it is certainly present inside the phagocytic cells themselves.

Now why it is deposited around fibers - well, I think it's the same process that we make use of to recognize the fibers. I think the important first stage is coating the fiber with mucopolysaccharide.

How this happens, why it happens and so on, we don't know. But it does seem to be that in this particular environment the fiber is partially surrounded by cells and you do get coating with mucopolysaccharide.

Now, one of the chemical things I can't explain is that colloidal iron seems to be attracted to mucopolysaccharide,

THE WITNESS: (cont'd.) and we make use of this actually in the pearl stain that I mentioned, because we want to see if there is iron-containing...sorry, if you want to see if there is mucopolysaccharide in the tissues. You actually use a stain of colloidal iron and wherever there is mucopolysaccharide your stain is stable.

I think what the body is doing, in fact, it's doing its own colloidal iron stain on these structures. When we want to recognize ferruginous bodies, we simply add more iron that we can see in a microscope.

I'm sorry. Is that...?

DR. UFFEN: Oh, very good. Thank you.

THE WITNESS: That is simply a longitudinal section of the body, an asbestos body. It's protruding through a surface of one of these cells - asbestos fiber here, layer of mucopolysaccharide. For some reason the hemosiderin when it begins to be deposited in the body moves fairly quickly in towards the asbestos fiber so that the first staining is always seen close to the fiber.

You can see that effectively this body is protruding from the cell, the giant cell hasn't completely formed.

Now I think it might be helpful to change the magnification and switch from electron microscopy to light microscopy, to demonstrate at least the process of asbestosis or fibrosis, and perhaps it will be easier. Today we'll talk about what happens to the fibers.

This is a slide of rat lung tissue at a magnification of only about five or six hundred. What you have here is the normal sponge-like structure of the lungs, the spaces are the airspaces or alveoli. Each has a pretty thin wall, and in these walls the small blood vessels or capillaries run, so that this is where oxygen transport occurs. Gas is inhaled and has to pass

THE WITNESS: (cont'd.) the shortest possible distance where it can reach the blood.

Now, as I've said, these alveoli walls are normally very thin. In order to function they have got to be as thin as possible, and that's where the disease process comes in.

The other thing you can see in this slide at the light microscope level this time, these are the phagocytic cells or macrophages absolutely stuffed with asbestos fiber. You can, in some of them, see a central blue spot. That is the nucleus that we talked about in the electron microscope specimens, surrounding the nucleus, the cytoplasm, and the granular structure you can see in fact are very large numbers of small asbestos fibers.

Here is a rather longer fiber that seems to be outside the cell.

The change to light microscopy has reduced everything in size.

Now, I think one of the important things about this photograph is that certainly a lot of cells having engulfed a great deal of asbestos remain in the alveolar spaces. They can remain there for quite a long time, or some of them undoubtedly escape into the larger air spaces and are eventually coughed up and removed from the lung.

But some of them certainly sit here in these spaces for a long time and they don't seem to do very much.

But the disease process of asbestosis involves the thickening of the walls of the alveolar sac. This is, again, a rat specimen treated with asbestos for a long period of time, and these much-thickened walls now correspond to the very thin ones that you saw in the previous slide. There is a great deal of asbestos present. You see granular material or an occasional obvious fiber.

I think the important process, the important thing

THE WITNESS: (cont'd.) to see from this slide, is that in this thickened wall there is the asbestos, so some of it having originally been deposited in the space, picked up by cells, has now got inside the solid tissue. I think this is most important in the production of the thickening of the alveolar wall, the formation of scar tissue in the alveolar wall, which is basically the disease asbestosis.

How the fibers get in...many of them, I think the phagocytic cells that have picked them up, these are mobile cells... I think they have got two possible pathways. Why they choose one and not the other I'm not sure. One pathway is the one I mentioned, to be out, coughed out and away. The other one is to burrow actually into the tissues, and that is obviously the dangerous pathway from the point of view of disease production.

So that is one...

DR. MUSTARD: Can I ask you a question? How active is the proliferation at such sites when those macrophages are present? Have people done studies to look at the turnover of DNA in the cells under such circumstances?

THE WITNESS: Not in those circumstances, no. It could be done if we labelled and injected the animals we label at that point. We could get a good idea of the multiplication rate.

DR. MUSTARD: I guess the question I would like to ask, and you may be coming to it, the current evidence is that macrophages, when they are stimulated, can synthesize and secrete mitogen, which for those people not biologically trained, will stimulate cells to proliferate. Has there been any study done about these macrophages under these circumstances, as to whether they do form and release mitogen, and if so, how long they are able to do it?

THE WITNESS: There have certainly been no completed

THE WITNESS: (cont'd.) studies, and I think you are right to point out that perhaps it's rather a pity.

We have in progress...

DR. MUSTARD: The evidence is only about a year and a half old, so it's not...

THE WITNESS: We have in process one project which I think might provide some answers to this. A lot of people, ourselves included, as you've seen, have studied long-term disease production. We are now starting to look at the biochemical effects at the early stages and we shall be doing this by exposing experimental animals to dust for relatively short periods of time, and then we shall be washing out the cells from the lungs, keeping washout fluids as well, and we shall be doing a lot of examinations on these cells and on these fluids, and we hope to look for mitogens to see if they may have been produced. We'll be getting a lot of macrophages with dust in them.

The project is not only going to be involved with asbestos. It's going to compare asbestos with coal and quartz, and some completely innocuous materials as well.

But, I'm sorry, we've only got started and I have no information at all. I agree with you, it's rather a pity that we don't know the level of miototic activity.

I think in the past many people assumed that the macrophages were end cells and they didn't divide when they were actively phagocytic. I think we now have evidence that some of them do. What we need is evidence of how often and how important this is.

DR. MUSTARD: My question is based on a very practical problem, and that is all the evidence that we have been given about the inhalation of asbestos fibers and asbestosis is that even when you take a person away from exposure to asbestos, the process tends to progress...presumably that you would be recycling macrophages, new macrophages, new stimulation to the

DR. MUSTARD: (cont'd.) process of cell proliferation.

But there is an interesting problem in this and a not totally different experimental circumstance where you damage the lining of an artery, another foreign element can come in and it, too, releases a mitogen which causes the cells in the vessel wall to proliferate. Of course some of us think that's the process of hardening of the arteries, but if you take away the injury stimulus and stop the cells coming in, not only does the scar development stop, it actually regresses.

I wondered in the pulmonary system if there is any experimental circumstance where you can initiate this kind of response and then there is...through some technique, I don't know how you would do it with asbestos fiber, stop the macrophages from interacting and whether you can (a) stop the proliferative response and (b) whether you might even get some regression of the lesion. There is a therapeutic implication of that if you could ever achieve it.

Has any of your work given you any insight into whether that is at all possible?

THE WITNESS: The simple answer is no. It would be very, very interesting to do.

I, like you, think that the progression of asbestosis, which you can demonstrate experimentally and we have been doing...

M. CASGRAIN: I can't understand. Can you speak a little louder? I can't understand.

THE WITNESS: I'm sorry. Where shall I start again?

We were talking about the progression of asbestosis and discussing whether or not it was due to the turnover of cells, perhaps the proliferation of cells in contact with the asbestos fibers.

The suggestion was if you could stop the turnover

THE WITNESS: (cont'd.) or proliferation of cells, if you would stop the disease process. I was asked if we had any evidence for or against this suggestion, and I have to admit we have none.

But it's a very interesting suggestion and it would be very nice if there was some experimental way to approach it...if we could stop the macrophages approaching dust after a certain point would the development of the disease stop.

MR. LASKIN: Q. As I understood it, the fibrosis results from this collagen production, and is there something in the macrophages, you indicated, that was significant, that the macrophages were under this tissue and is there something in the macrophages that are carrying the asbestos fiber that stimulates the production of collagen?

THE WITNESS: A. Yes. I mentioned this work of Professor Heppleston, and I said that he had undertaken experiments with macrophages exposed to quartz, but I think one or two people claim that you get the same results with asbestos. There is a little argument on this.

Professor Heppleston found that macrophages treated with quartz produced a substance, a factor he called it, a chemical, which when added to fibroblasts, collagen-producing cells, greatly stimulated their rate of production.

So that remained one possible way in which asbestos or other dust is able to stimulate the formation of scar tissue.

The other possibility that was suggested is that small amounts of asbestos actually get into the collagen-producing cells themselves, and we don't know the relative importance of this process.

DR. UFFEN: Are you going to be pursuing how it becomes cancerous?

THE WITNESS: To the extent that we've got some information, yes, I would like to take that up later.

Now, I think the next slide simply shows a more advanced stage where the originally thin alveolar walls now become very, very thick indeed, and that section of rat lung would be very little use for gas exchange.

This, of course, is why the disease of asbestosis is so dangerous. The lung ceases to function, ceases to oxygenate the blood and the patient develops severe respiratory disability.

Now, could I switch this off for a moment? I think it would help if I settle down here until I want to show some more slides.

Now, when I was invited to appear before this Commission to discuss the asbestos-related studies that we have been involved in for many years, it was indicated to me that there were two particular points that the Commission might wish to hear about and to discuss.

The first one was what value, perhaps what are the disadvantages of data obtained from animal experiments, and the second one was what do we know about the way asbestos fibers produce tumors.

I suggested to John Laskin it might be helpful if I presented a few of my ideas on these two points before waiting for questions and discussion on specific points you would like to raise.

So firstly, if we can tackle the subject of the value of animal experiments, do experimental animals react in the same way as humans when they are exposed to asbestos dust, and I did discuss this matter and the New York meeting in 1977.

I pointed out that while there were variations between animal species in the severity of their reactions, most of those that have been subjected to asbestos, most of those species

THE WITNESS: (cont'd.) subjected to asbestos a number of times, have produced the three main human conditions. That is to say only fibrosis or asbestosis, bronchial carcinomas, tumors formed inside the lung itself, and mesotheliomas - a rather rarer tumor that develops on the surface of the lung.

I pointed out at that time, at that conference, that of all the species that have been used, the rat produces these three conditions most readily and appears, as far as we can see, to be the best experimental model that's available.

Indeed, the rat, of course, has been most widely used for these studies.

However, as I discussed in another review article that I produced last year and you have been circulated with it, there is one way in which the rat appears to react differently to what is normally considered to be the human situation, the case with human beings. This is in the relative harmful effect of different types of asbestos - chrysotile or amphibole, crocidolite or amosite.

I think it's true to say that we have come to accept that for humans crocidolite is the most dangerous, and many people would say by far the most dangerous variety for human beings. Therefore, perhaps, it's rather surprising to look at all the animal experimentation that has been undertaken, whether animals have been treated by inhalation or the dust has been injected, that you find that by and large chrysotile has come out as dangerous as crocidolite. Indeed in many experiments it has come out as distinctly more dangerous than crocidolite.

On the evidence of animal experimentation, amosite seems to be the safest variety.

Now, those are the facts as they come out of animal experiments. What could be the possible reason?

Here, I think we are obviously speculating that there is some data available. I think the first possibility is

THE WITNESS: (cont'd.) that the doses to which humans are exposed to in relation to crocidolite, in the past, may well have been seriously underestimated. We do know that crocidolite is the type of asbestos that most readily produces a dust cloud. In a simple way, you can kick a bag of crocidolite and produce a tremendous dust cloud, whereas with chrysotile you tend to have to manipulate it quite vigorously in some industrial process to generate very much dust.

It could be that the dose levels in the famous crocidolite cases that we all know about - Chris Wagners reports from South Africa and the reports of gas mask workers - it could be that the crocidolite dose was much higher than we can imagine.

If that was the case, then the so-called excess danger from crocodilite was dose-related and type-related. Now, unfortunately, I don't think we will ever get really concrete evidence on this point, although I believe the South Africans have been looking back in their data and have produced some evidence that might indicate dose levels in the crocidolite plants of twenty, thirty, forty years ago were incredibly high.

But whether or not that is true, certainly one would expect crocidolite handling to produce much higher fiber counts.

MR. LASKIN: Q. Does that relate to the shape of the fiber?

THE WITNESS: A. To a certain extent it does, yes. Chrysotile fibers tend to be long and curly. Amphibole fibers tend to be perhaps equally long, but very straight. I think when you have a mass of chrysotile packed into a bag, the fibers tend to matt much more easily. This means that they need to be separated quite vigorously in order to produce a dust cloud.

The amphibole fibers don't matt nearly so well, and they are much more easily thrown up into a cloud.

Q. Is that true of amosite to the same extent as crocidolite?

A. As far as we can tell, yes. The basis for that statement is some studies we have undertaken in our animal experimental inhalation chambers.

We tried to see what was the maximum dust cloud we could generate with any of the asbestos types...maximum respirable dust cloud. That is to say, we used a dust sampler that was designed only to take in particles of the sort of size you would expect to penetrate into the human lungs.

We found that the maximum cloud we could obtain with chrysotile asbestos was about thirty milligrams per cubic meter - a fantastic cloud, true. But we could not get higher if we used extra generators and pumped more dust into the chambers. We simply produced a snowstorm, because the long, curly fibers actually matted themselves in the atmosphere and fell out as visible snowflakes.

We tried the same thing with amphibole dust, and we could easily get to a hundred milligrams per cubic meter, and that's where we stopped. We don't quite know what the maximum would be with amphibole. But certainly you can generate a much higher respirable dust cloud with the amphibole types of dust.

Another possibility for the apparently different results obtained in rats and human beings could be that the dusts used in animal experiments have had rather different particle size and shape to those that you find in human exposure.

Now, the importance of this particle size and shape we will be dealing with in more detail later, but certainly there is some evidence that this could be true in that we do know that the UICC reference asbestos samples, the ones that most people tend to use for experimental studies, were very finely ground indeed and can be shown, on average, to have rather shorter fibers than you can collect from industrial situations.

So it could be that we are not comparing...we are

THE WITNESS: (cont'd.) comparing experiments with identical asbestos types. It may be that we weren't using dust clouds that were strictly comparable because of differences in the particle size. That was another possibility.

The third possibility, and maybe this is the most important point, is that indeed chrysotile is potentially the most dangerous asbestos variety. But it is also the variety that breaks up most readily in lung tissue, and as I'll be showing later, we have got some evidence that this is possibly the case.

Now what could very well be happening in the animal experiments is that your potentially very dangerous chrysotile could remain in the rat lungs for the two years of their lifespan which you need to produce tumors, but given ten years...and the humans probably need twenty or more years to produce the tumor...but in ten years the chrysotile may have broken down and most of it may have been removed from the lung tissue. So that the human may be able to get rid of the potentially dangerous chrysotile before harm actually occurs.

I think there is quite a bit of evidence on this score when you examine publications that have appeared, people have looked at the content of asbestos dust in the lungs of exposed human beings. There have been quite a number of publications by people like Fred Pooley in Cardiff, but the French seem to have been particularly active in this field and I think most of the publications have come from their groups.

I think it would be fair to summarize the results as saying that you always find in a human lung much less chrysotile than the exposure evidence you have would lead you to believe ought to be there. Much less chrysotile and, percentagewise, much more amphibole.

So it could well be that chrysotile potentially to biological systems is the most dangerous, but it is also the

THE WITNESS: (cont'd.) most easily broken up and removed if you give it time.

DR. UFFEN: When you say broken up, do you mean a physical breakup or a chemical breakup?

THE WITNESS: I think the answer might be both. Certainly I mean a physical breakup, but the physical breakup may depend on preliminary chemical reactions.

Would you like to...

DR. UFFEN: Rather than interrupt you now, perhaps we could pursue that later in the question period.

THE WITNESS: Yes, if you would like.

MR. LASKIN: Q. Just...and I don't mean to interrupt you either...but just on that explanation that you have offered, do I take it that that explanation depends on the proposition that the development of tumors really has some relation to an animal's or an individual's lifespan?

THE WITNESS: A. Yes. Thank you for bringing out that point.

I think it's fair to say that in any species with naturally-occurring tumors and experimentally-produced tumors, by far the majority of the tumors develop in the elderly animal, the elderly human being. So there is something about the aging process which makes tumor production much more likely. Certainly in experimental circumstances it's fair to say that you need a significant portion of the whole lifespan of the species.

Now, your rats, the maximum we can keep our rats going for is three years. So that is the absolute maximum of time for tumor production. In fact, most tumors will be developed in eighteen months, two years, two and a half years.

Of course, human tumors we would probably expect the production period to be twenty years, thirty years, forty years. Indeed there is evidence with the asbestos tumors, certainly

THE WITNESS: (cont'd.) mesothelioma, that they can develop forty years or more after first exposure. So it does seem we are dealing with some sort of roughly equivalent fraction of a total lifespan.

Q. But I take it you would expect that the time for breakup of chrysotile on this proposition would be the same, or roughly the same, in animals as it would be in humans?

A. That is my suggestion. There is relatively little definite evidence on this, simply because up until now I don't think many people have examined the situation. We certainly do know that there is some chemical dissolution of chrysotile in lung tissues. I think we've got evidence of some breakup. At this point one would simply make the assumption that because this tends to be chemical rather than biological, physical rather than biological, that it would probably occur at a fairly constant speed.

Q. And would therefore take place over most of a rat's lifetime and a very short percentage of a human's lifespan?

A. This is the suggestion.

But to go on from there, these are statements of the value of animal experiments and I think I've indicated that right at this time we might not be able to extrapolate exactly from rats to human beings comparisons made with chemically different varieties of asbestos, because the possibilities they would breakup would be clearly different rates.

However, it must be remembered that rat studies do indicate that both chrysotile and the amphibole asbestos types are both or all exceedingly fibrogenic and exceedingly carcinogenic. So the rat is agreeing very well on the general principle and perhaps we are getting slightly differing opinions on exact comparisons.

We have learned a very great deal from animal

THE WITNESS: (cont'd.) experimentation, and I think we can certainly continue to do so in a number of specific ways that I might mention.

Firstly, in the field of asbestos substitutes... people, of course, for many years have been trying to replace asbestos useage with substitutes, manmade mineral fibers are perhaps the best known. Now, I think if anything the rat is more sensitive to asbestos than humans, certainly we can produce tumors in very large quantities. I would suggest if you are testing asbestos substitutes in rats and get a negative result, completely negative result, then I would certainly trust this result.

The difficulty would be if you got some tumors. It would be very difficult to extrapolate dose back to human beings and say the safe dose of this fiber is so much. But certainly if you wanted to assure yourself whether a material is likely to be completely safe, if it can pass the test of the rat I would back it to be safe for human beings.

DR. MUSTARD: Can I ask you a question about the rat? I presume that these are inbred strains of rats which you are using?

THE WITNESS: Yes. No. The type used for inhalation studies is a strain of AFA hand rats, which are crossbred.

DR. MUSTARD: Yes, but they are still a laboratory strain of rat?

THE WITNESS: They are still a laboratory strain of rat.

DR. MUSTARD: The question that comes to my mind then, if you took...if you could get ten different strains of rats which were not genetically related, would they show any differences in response? In other words, are there some strains that are more susceptible than others?

THE WITNESS: This has been looked at, I think by

THE WITNESS: (cont'd.) Chris Wagner in New South Wales, and I think he has produced one publication...I have certainly seen the data...and there is some indication that there is variation amongst rat strains. As far as absent percentage of tumor production is concerned, there is no evidence of significant variation - for example, one strain not producing any tumors or very, very few. But there is certainly some numerical variations which appears to be statistically significant, between the strains.

DR. MUSTARD: Has anybody tried to explore why within one strain of rat only some of the rats come down with tumors?

THE WITNESS: This, of course, raises the subject of individual susceptibility. We are aware of the problem.

You say has anybody tried to explore? I think the answer is no, because I'm not sure that anybody has thought of a successful experimental approach. It is certainly the problem of all carcinogenesis. I would imagine there are individuals in the human population who are much less likely to produce tumors than others. We don't know how to find them or why this is.

DR. MUSTARD: If I can pursue this a step further, the humans that are exposed to asbestos, of course, are not inbred strains. They are a random sample of the population. Therefore you would range from highly resistant to highly susceptible, theoretically. Would that not be another explanation for the difference in the results of the rat data versus the human data, as you are dealing with one with a fairly homogeneous genetic strain which you have targetted on because you can produce effects in, versus the human population in which you have no genetic control.

THE WITNESS: It could be. One would have to assume that the genetic differences we talk about made the

THE WITNESS: (cont'd.) susceptible individuals particularly susceptible to one asbestos type rather than another. That might be a little difficult to believe. I can well imagine that there would be individuals whose genetics made them particularly sensitive to asbestos or fibers in general.

But you may well be right. It's possible that the genetic (voice fades out here...half a dozen words inaudible.)

DR. MUSTARD: But is there any evidence that in animal experiments that some strains take a longer time for effects to be produced than others? Which would tie back into the genetic susceptibility question.

THE WITNESS: As far as the rat is concerned?

DR. MUSTARD: Yes.

THE WITNESS: I am sorry, but I cannot remember Chris Wagner's data exactly. I know he got differences in numbers of tumors. It may be that he got differences in timespans. I'm sorry, I don't know.

DR. MUSTARD: I don't know of any evidence for it either, but I'm just curious as to whether it did occur.

THE WITNESS: It could well do so.

But if I can continue discussing the point of animal experimentation where it could be useful...

DR. DUPRE: Could I perhaps, Dr. Davis, just interrupt at this point because what you have...you may be continuing on with exactly the points you were making, but just in case you are not something did go through my mind as you were speaking a moment ago.

It's simply this. As I take it from your own review of the literature, the animal experimentation results where different asbestos fiber types are concerned basically show little difference in the hazardous nature of the fibers...perhaps, if anything, chrysotile may appear somewhat more dangerous... whether the study was an injection study or an inhalation study.

DR. DUPRE: (cont'd.) Is that correct?

THE WITNESS: Yes, that is basically correct.

DR. DUPRE: And if that is basically correct, one of the things that interested me very much in your 1981 paper, which for the purpose of the reference system we use here is number seventeen in the exhibit that contains your writings...this is the paper entitled Biological Effects of Mineral Fibers. Are you with me?

THE WITNESS: Yes, that's right.

DR. DUPRE: I was simply very interested in reading that paper to note on page 231 your observation that it would appear that where glass fibers are concerned...there we are into a possible substitute...there is a difference between the injection and the inhalation studies, and that apparently glass fibers appear to be hazardous when injected directly into the pleural or peritoneal cavities, but apparently...as you point out in the very bottom sentence on that page...so far inhalation studies with glass fibers have shown little tissue reaction at all.

Do you have any speculation to offer on the reason there?

THE WITNESS: Firstly, I would say that those statements that you have indicated were certainly true as far as I was aware at the time they were made.

I think we've got a little more information now. The early studies, as I indicated, of glass fibers produced nothing. As you know, there have been quite a lot of studies recently, and certainly Chris Wagner in Cardiff has been undertaking a big series of inhalation studies with glass fiber for the manmade mineral fiber industry.

As you know, there is a conference in Copenhagen in April where they are trying to tie together the results of a large number of research projects on manmade mineral fiber.

THE WITNESS: (cont'd.) I believe it's fair to say, I have been told by Chris Wagner, he is getting some degree of pathology from glass fiber inhalation.

As far as the exact details are concerned, I know he is waiting until the Copenhagen Conference to produce that.

But it may be that after Copenhagen we will be saying early experiments produced nothing, but the latest ones have and we may have some indication of a reason.

I am sorry to be uncertain about that, but certainly it did appear that the early studies by inhalation produced nothing.

Maybe the fiber if we get...although I know in some of the studies...I believe the study of Lee, of a later study, he used very high doses, got enough dust material into the lungs to cause quite a bit of early damage - alveolar proteinosis - indicating that the alveolar walls had been damaged from the dust imposition, but this just didn't progress into fibrosis or anything more serious.

Why, I......no explanation was really offered. One possibility is that glass fiber actually breaks down relatively quickly in the tissues. You might not imagine this, but I think it's a possibility that should be considered.

DR. DUPRE: Indeed, I was speculating on the extent to which some of your own hypotheses that you have for explaining to me what happens in the different fiber type situations might be applicable to glass fibers. With reference to the inhalation studies, for example, is it possible that the aerodynamics of glass fibers is different from the aerodynamics of asbestos fibers.

THE WITNESS: If the fibers are the same length and diameter, and the same density...and the density I am not sure about because I am not a physical chemist, be sure of this...then I'm

THE WITNESS: (cont'd.) sure in air they would behave the same way. They would reach the same position in the lung if their length and diameter and density are the same.

Certainly we know that length and diameter of many glass fibers can be the same or very similar. Certainly the amphibole asbestos variety. Therefore you would expect that type of fiber to get into the lung tissue.

With regards to glass fiber of fiberglass, or manmade mineral fiber use in general, I'm sure it's true to say that in the early days, and to a large extent now, much of the fiber is far too thick to possibly get into the lungs.

So that the real question is, is modern manmade mineral fiber going to have a sufficient percentage of the very fine fibers amongst the general mix to produce a potentially dangerous dust cloud.

I think there are, in the more modern manmade mineral, there are some of the finer fibers present. These are ones used for large industrial processes. The question is, is there going to be enough of the fiber.

But experimental work, a lot of it, has been done with the rather unusual, very fine type of preparations that have been introduced. I think the best known series was produced by Johns-Manville in the United States. They produced a series of glass fiber (a few words inaudible)for industrial production, but they had a wonderful series, the finest of which Chris Wagner is using, amongst others, break down many of the fibers down to the asbestos range, and certainly with that variety it was possible to produce a cloud and I imagine you could get as many fibers into the lung as a cloud of asbestos.

I don't think that fiber is in any industrial useage at the moment, probably because it's too expensive to produce.

DR. DUPRE: I can take it though, I gather, that in the injection experiments the dimension of the glass fibers that have been injected would be fine dimensions? They would be of a dimension that would easily be inhaled?

THE WITNESS: The problem, of course, is that... especially with glass...that to produce a dust cloud for inhalation the lung selects its own sizes. If things are too big, they won't get in at all.

If you take the original glass material and you inject some of it, inevitably you've got to inject all the fiber that is there so that you will have some fiber that will be too thick to be inhaled. I think that's inevitable.

But you will also, of course, have all the fibers that are small enough to be inhaled.

The best experiment was done with things like the very fine Johns-Manville dust that had eighty or ninety percent of fiber within the respirable range. Then you were left with a few too thick.

But it is one of the limitations in injection studies that you have to put in the whole sum.

If I can continue, I was discussing ways that I think we could get valuable information from animal studies.

A second way that I would like to suggest is we can still explore the importance of variation in particle size and shape, and we will be discussing this more later on.

Here I would simply like to say that if experiments were conducted between chemically identical samples of asbestos, which differ only in their physical size, then I'm fairly sure the results obtained from that would be fairly directly extrapolatable to human beings.

In other words, if the rat indicated that one particular fiber length was the dangerous one, then I would

THE WITNESS: (cont'd.) certainly expect that to apply to human beings as well.

DR. UFFEN: But there are no major differences in the passage getting down to the lungs, between a rat and a human?

THE WITNESS: There are differences, but I don't think they have any great effect at the sort of sizes we are talking about which, as we'll indicate later on, are probably a question of whether a fiber is ten microns long or twenty microns long or thirty, perhaps. I don't think you would get major differences in particles of that size.

Another way that I was going to mention, possibly the effect of chemical treatments. I know that at the present time there are a number of chemical treatments being considered, certainly for treatment of chrysotile, that may or may not affect the harmful nature of the dust.

I think there are other reasons for the treatment as well. They may have industrial advantages as well.

But I think if you are comparing treated and untreated samples of exactly the same type of asbestos, you probably would get results from animal experiments that you could rely upon unless...and here we come back to the same caveat...the chemical treatment is such that it would actually affect the breakup of fiber. This is something one would have to check on.

I think I would indicate at this point that one field of research that I think will be most important in the next few years is for us to look at the breakup of fibers in lung tissue...evidence both from experimental animals where we can control the situation, and what evidence we can get from the human situation. We do need to know what happens to the fiber in the lungs as far as breakup - splitting longitudinal or transversely is concerned. This is a field that I think has been relatively ignored in the past.

THE WITNESS: (cont'd.) So that was a little summary, perhaps, of some of the problems of animal experimentation and some of the things that perhaps we should be thinking about for the future.

The second question...

MR. LASKIN: Would the Commission, and perhaps Dr. Davis, wish a short recess?

DR. DUPRE: I think that might be entirely appropriate, counsel. Dr. Davis has been going at a wonderful pace here.

Shall we break for maybe ten minutes?

MR. LASKIN: Sure.

THE INQUIRY RECESSED

- - - - - - - - - - - - -

THE INQUIRY RESUMED

MR. LASKIN: Are we all set, Mr. Commissioner?

DR. DUPRE: If you please, counsel, will you resume?

MR. LASKIN: Dr. Davis?

THE WITNESS: Before the recess, I was about to tackle the second question that we indicated earlier, and that was what information have we on the way that asbestos fiber causes tumors.

Now, I think it depends exactly what you mean by that question. If you mean what exactly is the reaction between the fiber and the cells by a chemistry that causes a cell to become a cancer cell, then I think we've got to say simply we've almost no information at all. But equally, we've almost no information at that sort of level about any type of carcinogenesis. We simply do not understand the normal control mechanism of cell division in that sort of detail. We do not understand exactly how a cell is told to switch on and divide at a certain speed for a certain length of time, and then stop again, which happens in

THE WITNESS: (cont'd.) the normal body.

So at that sort of level we know nothing about asbestos carcinogenesis.

If on the other hand you mean what are the parameters of asbestos dust that are most important in tumor production, then we do have quite a lot of information. I think first of all we can say that all attempts to relate asbestos carcingonesis to the identity, the chemical nature of the different asbestos types has completely failed. There seems to be no evidence that the chemistry of the fiber is at all important.

In addition to the actual chemistry of the fibers themselves, there has been work done on the chemical contaminants of bulk asbestos samples. One of the best-known pieces of work in this field related to the fact that it was shown that certainly some chrysotile samples, the bulk samples, coming out of the asbestos mills contained quite significant amounts of the chemical benzpyrene, which is one of the best-known chemical carcinogens that there is.

Now, this benzpyrene could be shown to be absorbed very strongly onto the asbestos fibers and quite naturally it was suggested that maybe the carcinogenic potential depended on this... the contaminant and not the asbestos.

But work was done by a number of people in which they very carefully extracted all the benzpyrene from asbestos samples and compared the carcinogenic effect of extracted and unextraced samples, and the results were identical.

It did not appear that the benzpyrene had any effect at all.

I think it's true to say that at the moment it is generally accepted that the important factor in asbestos carcinogenesis is the size and shape of the fiber. Now, a number of workers have studied the importance of this, going back I think

THE WITNESS: (cont'd.) to the earliest paper by Professor King, I think, in 1946. He showed that long-fiber asbestos samples that he had prepared by cutting them in a special machine were more...produced more scar tissue, more fibrous tissue than short-fiber samples. So that the idea that long fiber might be more dangerous than short goes back as far as 1946.

It was years later when the same sort of finding was made in relation to tumor production, and I think the most important work on this side of things was undertaken by Merle Stanton and his group in the United States of America.

This group, of course, has published a number of papers over the years. They examined the carcinogenic potential of a large number of different samples of fibrous dust, which they injected or implanted into the pleural cavity of rats.

They carefully measured the particle size distribution of the dusts they implanted and they very carefully analyzed the data, the number of tumors produced, in relation to the particle number and particle size of the dust implanted, and they came to the conclusion as a result of this detailed analysis that the most carcinogenic fibers were those longer than eight microns and thinner in diameter than about one point five microns.

At least that was the figure given in the early papers. I notice that in the last paper that Stanton's group produced they were indicating that the most carcinogenic diameter was actually less than that, and they were suggesting something down to point two five of a micron.

But basically they were showing quite clearly that the most carcinogenic fibers were relatively long and pretty thin.

But from all those studies the important piece of information that came out was again that the chemical nature of the fiber didn't seem to matter, whether it was chrysotile or

THE WITNESS: (cont'd.) amphibole...or indeed many of their studies were undertaken with glass fibers. Tumors were produced with all.

DR. UFFEN: Do you mind my just drawing attention to a comment here, because I would like to be quite clear on this one in what is listed **as** our exhibit number twenty-six and which was in 1980: It's the Use of Animal Inhalation Experiments in the Study of Asbestos Bioeffects.

The thing that is troubling me is your very last sentence, and what it says is: "Much more data is necessary,

> but it's present in rats at least. It would appear that while long, thin fibers may be essential for tumor production with any asbestos type, the fiber chemistry also plays an important part".

Now, that's 1980. It is 1982. Am I hearing you correctly that you didn't say that now?

THE WITNESS: I think you are probably right in picking out a point there that I have used the word 'fiber chemistry' more loosely than I would like to do, and I think the statement that I made there would certainly be more applicable if we talked about speed of fiber breakup, which may well be related to the type and therefore the chemistry.

But certainly, thank you for pointing out that anomaly.

The point I was making that in Professor Stanton's work it did appear that the fiber type, chrysotile, amphibole or glass fiber, didn't matter very much...it was the length and diameter of the fibers that were really important.

Now, in one of his early papers Stanton pointed out that while it was fairly obvious that the long, thin fibers were the most carcinogenic, the tumor incidence didn't correlate

THE WITNESS: (cont'd.) terribly well with the actual numbers of long and thin fibers in a particular sample - not as well as he might have liked them to. And he did suggest that he got a much better correlation if he produced a figure from the theoretical number of long, thin fibers that could be produced if all the bigger fibers broke down into their possible subunits.

In other words, if you had a bundle of chrystals - as you do with asbestos - if you imagine them breaking up into the theoretical number of subunits, this correlated better with tumor production.

Now, this idea wasn't taken much further by Stanton. I think the reason was that a lot of his later experiments were undertaken with glass fiber where the fibers do not exist as bundles and are not capable of breakdown. He used glass fiber in so many of the later experiments because he was able to get better-controlled fiber sizes than was possible with asbestos, and therefore he believed this was a more acceptable experimental material for dealing with tumor production from fibrous minerals.

However, although this idea of Stanton's was not taken further at the time, I think it is an important one and I think it does tie in with some of the work we have undertaken recently in Edinburgh. In this respect at this point I would simply like to pick out two publications...rather two experiments... the first of which was published in 1978, and the second of which was presented at the Cairo Conference this summer on occupational medicine, and therefore since the Conference report isn't out, has not yet appeared in print.

In the first of these two studies we examined the effects of both mass and fiber number on the harmful potential of asbestos, using the UICC reference samples.

This has been circulated. I probably remember the results, but perhaps it would be helpful if I simply put

THE WITNESS: (cont'd.) on the board the relevant data which we've got in slide form.

MR. LASKIN: Q. Is what we have as tab number ten, the article...

THE WITNESS: A. That is correct.

MR. LASKIN: ...in the British Journal of Cancer.

THE WITNESS: Now, in this experiment you'll see we approached the idea of mass versus fiber number by taking the three standard samples - chrysotile, crocidolite and amosite - and exposing rats at the same mass of ten milligrams per cubic meter. We then reduce it, since amosite had the largest fibers, we reduced the mass of chrysotile and crocidolite in separate experiments to the level at which we calculated we would have the same fiber number as ten milligrams of amosite.

You will see in the column of fiber number that we didn't get things exactly right. Experimental conditions seldom are. But we got the numbers reasonably close - 550 per ML, 390 per ML, 430 per ML.

DR. DUPRE: May I just interrupt for a moment, Dr. Davis?

Counsel, is that...have you found that table under tab ten?

MR. LASKIN: No, but I've seen that table.

THE WITNESS: I'm sorry. That should be in number ten. It's not there.

DR. DUPRE: Number ten is the article entitled Mass and Number of Fibers?

THE WITNESS: That's right. It should be there. There's been a page been missed out. I didn't look at this. It should be there because...

MR. LASKIN: Actually, it appears as table number one in tab twenty-six.

DR. DUPRE: Oh, in tab twenty-six?

THE WITNESS: I have probably reproduced that number occasionally.

MR. LASKIN: Yes, I think you have referred to it.

THE WITNESS: This is where it first appeared.

DR. DUPRE: Yes, I see it. It is indeed in...at page 454 of your tab number 26.

Thank you, counsel.

Excuse me for interrupting, Dr. Davis.

THE WITNESS: In the column of fiber number, I should point out that we estimated fiber number in the way that is estimated in factory dust counts.

That is to say, we counted fibers visible in the phase contrast light microscope and counted as a fiber anything more than five microns in length as long as it had an aspect ratio, a length-to-diameter ratio, of greater than three to one.

So these are the fibers that would have been counted in the factory.

You will see from the simple summary of results as far as fibrosis is concered, the first three columns, you can see there is no relationship to dust mass...the chrysotile ten milligram cloud is much more fibrogenic...and not very much relationship to fiber number in that, if you compare the bottom three sets of figures, well, amosite and chrysotile may be close enough for experimental difference, but crocidolite produced almost no fibrosis.

We come along to the number of lung tumors produced and you will see that compared to mass, the chrysotile produced many more tumors and produced the only malignant tumor.

If you compare fiber number, the bottom three sets of figures, again it's the chrysotile that stands out.

Now, at the time we suggested that the possible

THE WITNESS: (cont'd.) reason for this came when we examined the dust clouds with the scanning electron microscope and estimated the counts in a slightly different way. We produced fiber length distributions, percentage number of fibers at each length compartment, and we found that the chrysotile cloud actually had a much higher proportion of fibers that were over ten, certainly over twenty, microns in length.

So that counted as they would be counted in the factory, our fiber numbers were relatively close. Actually, if you consider the number of the longer fibers - over ten and certainly over twenty microns - the chrysotile cloud had the highest number of these long fibers.

Now, at the time we suggested this was the explanation for the apparent excess danger from chrysotile. I still think that that was part of the reason, but I think there was an additional factor which we certainly didn't appreciate at the time of this publication. This came out as the result of another study that we undertook, and this was using dust from chrysotile material prepared by the wet dispersion process.

Now, is this a process that is well-known, or would it be helpful if I very briefly summarized?

MR. LASKIN: I think it would be helpful if you briefly summaried it.

THE WITNESS: The wet dispersion process, basically, involves taking the raw chrysotile material from the mill and treating it with a mixture of detergents. This is a process undertaken by many different companies throughout the world, and I believe the actual mix of detergents is very often a company secret. But by and large chrysotile is treated with detergent which causes the bundles of fibers to separate, so that the relatively-thick bundles separate out into all the little individual fibrils that I have been trying to show you this morning.

THE WITNESS: (cont'd.) You've got a very fine slurry that almost looks as white as milk and about...not too much more dense than that...halfway through this process.

The end of the process is that if you now treat the slurry with an electrolyte, chemical electrolyte solution - and again, the exact solution varies from company to company - the fibers are then stuck together again...apparently, from a chemical point of view, much more firmly than they originally were.

However, they certainly are not stuck together again beautifully lined up in bundles as they were. It is now a felted mass.

The industrial process is useful in the following way: The slurry is extruded from a nozzle and the electrolyte solution is applied at the nozzle so that you actually extrude... the process works so quickly...that you actually extrude a yarn of this reconstituted asbestos. It's naturally a rather wet, loose structure to start with, but when it is dried out and spun you produce a textile yarn which has the advantage from the industrial point of view that it really is much tougher and longer-wearing, so I'm told, than standard chrysotile yarn.

From the health point of view, it has attracted attention from the obvious fact that handling this material produces very much less dust than standard chrysotile. Factory counts of areas handling the wet dispersed chrysotile usually are very, very much lower than the same type of process, weaving process, using standard chrysotile.

So that is the process. Now, we undertook some inhalation studies with it because we wanted to look at all types of asbestos to try and learn a little bit more about the asbestos bioeffect, how asbestos reacted in the tissue.

The first thing was that we managed to convince ourselves very easily of the truth of the idea that it's very

THE WITNESS: (cont'd.) difficult to generate dust from wet dispersed chrysotile.

I told you earlier that with UICC chrysotile the maximum cloud that we could generate was about thirty milligrams per cubic meter. We found with wet dispersed chrysotile the maximum we could possibly produce was four milligrams per cubic meter. Try as we would, we could not get above that level.

That being the case, we decided to undertake the experiments at four milligrams.

The dust material looked very different from standard chrysotile or UICC chrysotile, and I think the next two slides ought to indicate this.

First, this is the wet dispersed chrysotile. This is a picture taken with a scanning electron microscope and the importance will be more obvious when you see the second one in comparison. You can see that you've got relatively few pretty long fibers. These are about two hundred microns in length, and five microns or so in diameter.

Some of them, theoretically, would not be respirable, but relatively few fibers.

For a comparison, you have UICC chrysotile put up in the same way, taken at the same magnification. You do get an occasional long, thin fiber up to two hundred microns, but the majority of the dust, as you can see, is much smaller...many, many more particles present.

Now, since we had only four milligrams per cubic meter of dust and since the fibers were so relatively few in number, you expected the dust to be quite innocuous. We were rather surprised at the end of the study to find that our four milligrams of wet dispersed chrysotile had actually produced more tumors and as much fibrosis as ten milligrams of UICC chrysotile.

Our statisticians say that the tumor numbers were

THE WITNESS: (cont'd.) not significantly different although there were several more with the wet dispersed chrysotile, but nonetheless if you accept them as the same number, it means that four milligrams of wet dispersed chrysotile is as bad as ten milligrams of UICC chrysotile.

Now, what was the reason for this? I think we probably discovered the reason by doing some transmission electron microscope examination of the lungs of the animals treated with the wet dispersed chrysotile. This is shown in the next two slides.

Sorry, firstly that is simply a follow on fiber length distributions of those two dust clouds I just illustrated.

Measurements done with the scanning electron microscope...this shows the percentage of dust fibers greater than a certain length in the two dust clouds. Wet dispersed chrysotile is at the top, and UICC chrysotile is at the bottom.

I think these are the two points that are of great interest. With the wet dispersed chrysotile, if you follow that across, you can see that over twenty percent of the fibers were more than twenty microns in length. Whereas with UICC chrysotile, something like two percent of the fibers were over twenty microns in length.

That is simply a summary of the data I mentioned, of the number of tumors produced in these two studies.

We did, in fact, have two sets of wet dispersed chrysotile-treated animals and we compared the tumor number results with chrysotile at ten milligrams and chrysotile at two milligrams. You will see that as far as the adenomas, which are benign tumors, are concerned, the numbers were very similar in all groups. With the malignant tumors you can see that adenocarcinomas, squamous carcinomas, mesotheliomas, the numbers with the wet dispersed chrysotile were higher than the ten milligrams of UICC

THE WITNESS: (cont'd.) chrysotile and very much higher than the two milligrams.

I believe that's simply a summary of the results I was talking about.

Now, these are the transmission electron microscope photographs that I mentioned. I'm sorry, I know these are a little bit light for these light conditions, but what we discovered in the lungs of these animals was that there were absolutely no bundles of fibers left. Everything...no masses, no flakes...everything had broken down into individual fibrils.

Now, with cutting of very thin sections...fibers running in all directions...many of them would be cut, naturally. Occasionally you expect by luck to get one running in the plane of the section.

In some of these you can see individual fibrils that are really quite long. They are...that one I think is the longest and we measured that at ten microns. So some of these individual fibrils are in the fiber length that Stanton claims is the most dangerous, the most carcinogenic.

I think what was happening with the wet dispersed chrysotile was that although the process would chemically have stuck the fiber back together in what appeared from an industrial point of view to be a stronger way, when put into physiological fluid in the lung tissue the fibers that had been originally separated found it much easier to separate again.

So that the relatively few fibers, big ones, that got into the lung tissue, relatively quickly break down into their individual subunits producing very, very large numbers of fibers.

On this basis of fiber number we would certainly expect that we've got more individual fibrils there in the tissue than we would have done with the UICC chrysotile.

DR. UFFEN: I have a small confusion. If this is a very thin section, how do we know that those small ones aren't just looking at an end-on, or you know, if they are in a random...

THE WITNESS: Yes, that is quite possible. We can't be sure. All that we can say is that the ones that appear long, we've got that amount of them within the plane of the section. So when I said that that length is ten microns, we know that's the minimum length. So fiber could be continuing, it could have gone out of the plane of the section. Those little ones could be long fibers cut in transverse section.

DR. UFFEN: That's my submission.

THE WITNESS: But there is no way...

DR. UFFEN: There is no way to say that there is a large proportion of small fibers, then?

THE WITNESS: No, I didn't make that point for that reason. We probably have, but that section could not be given as evidence definitely to prove it.

What it can be used as is evidence firstly that the fibers are breaking up into individual subunits, and secondly, that some of those subunits are at least ten microns in length.

DR. UFFEN: I still am a little puzzled. If these things are matted together, they are not all aligned in the same plane by the time you get to use them. So if I take a matt and tear it on edge and then slice through it and take a picture, all I'm going to get is a bunch of little things just like that. So it could still be matted.

THE WITNESS: No, I think the actual recombination effect is very much closer than that in bringing things back into physical contact.

Now, if we go back the point to remember is that... back two or three...these are the big fibers that were in the dust cloud. Now, magnification is such that each one of those

THE WITNESS: (cont'd.) would certainly be made up of many...let's say a minimum of fifty subunits, and the point I was making is that you no longer find fibers of anything like that dimension in the lung tissues. They have broken down.

The only thing you now find is the individual subunit.

I think my last slide was simply showing that at rather higher magnification. Again, I'm sorry that the light isn't quite right.

This is showing an area of fibrosis and you can see individual chrysotile crystals, but they are lying parallel... I don't know if that's important or not...to collagen fibers, and it's a useful demonstration that the subunit of chrysotile happens to be about the same size as the collagen fiber.

Again, the point there is that the individual fibril is separate.

That is the last slide I have.

I think from that evidence we are getting to the stage where we ought to put more and more emphasis on what happens to the fibers in the tissues, and by fibers I mean relatively large ones that undoubtedly start off in the atmosphere.

I think we are probably going to find that the damaging potential depends on the number of fibers in the critical size range within the tissue, and because of this breakup it will be very different from the number of fibers we measure in the atmosphere.

With wet dispersed chrysotile it is logical to suggest that because it separates so easily the number of individual fibrils produced is quite fantastically large. Hence, it's excess danger, apparently to the rats.

Now, here we've got to digress backwards to the suggestion I made that the difference between rat and human

THE WITNESS: (cnt'd.) reaction may depend on the speed of time of breakup of fibers.

The results certainly indicate that wet dispersed chrysotile is more dangerous a material to expose rats to than standard chrysotile, but the very fact that this appears to be due to separating the dust out into individual fibrils, the finest possible subunits, I think means that these finest possible subunits are the most likely ones, given time to break up completely, and therefore I would not interpret this information was suggesting that the wet dispersed chrysotile is going to prove particularly dangerous to human beings. I think it may be in a form where it most easily breaks up and can stay in the rat lung long enough. But if the human lung does deal with chrysotile by somehow breaking it up within the safe time period within the safe time period of human species' lives, then the wet dispersed chrysotile would be just that much more easily broken up or more easily removed.

DR. DUPRE: So you are back at the hypothesis then, Dr. Davis, that the rats simply do not live long enough...

THE WITNESS: That would be my suggestion, yes.

DR. DUPRE: ...for the breakup to take place.

THE WITNESS: That is right. Not enough breakup... I'm sure some does occur...

DR. DUPRE: Is that a chemical process, the breakup?

THE WITNESS: Well, let us discuss that. I think there is some chemistry when we are dealing with chrysotile. Certainly it can be shown that in physiological fluid and even more rapidly in weak acid solution, the magnesium ions..and of course chrysotile is a complex magnesium silicate...the magnesium ions can be leached out of the structure and this initially is a chemical reaction. You are still left with a fiber that looks much the same, but chemically it can be shown to have much less

THE WITNESS: (cont'd.) magnesium. It ends up, effectively, as amorphous silica.

Now, I believe chemists agree that this should be a much more fragile fiber when it contains magnesium, and therefore more easily broken up physically at this point. So it may be that the breakdown process starts as chemical, the removal of magnesium, and then we are left with something that is physically weaker.

MR. LASKIN: Q. What do you mean by breakup? What is the significance of breakup? Does that hasten its removal from the lung?

THE WITNESS: A. Can I just deal with that for a minute?

I suppose by breakup I mean both the length and diameter. If we start off with the fairly big fiber with many, many subunits, I suppose it's fair to say that splitting that up into individual ones as probably happens with wet dispersed chrysotile at one stage of breakup, it probably increases the danger.

But then you've got something so thin, maybe more easily reactive to the body's chemicals, but I think its structual strength, torsional strength would be reduced, and then I think you would get it much more easily cracking up into pretty short lengths.

I think certainly, both from the physical point of view, those short lengths are much more easily removed. It is even possible that you get to the stage where the short length of amorphous silica may dissolve completely. I don't know the answer to that one.

But certainly I think once you have cracked them down into these short lengths one macrophage can remove many of them, and whereas a macrophage containing long fibers may be

THE WITNESS: (cont'd.) physically incapable of movement because long lengths are so difficult to remove, with short fibers they may find it much more easy to escape and clear them from the lung.

This is a subunit and they are much more...this is the dual process that I was talking about.

MR. LASKIN: Q. Looking at it from the other side, is there some hypothesis or proposed explanation as to why the long fiber is apparently the dangerous fiber?

THE WITNESS: A. In my interpretation of the matter there have been one or two suggestions, and I could summarize them.

Some people have suggested what is fairly obvious - if you have a cell that you have already demonstrated containing short asbestos fibers, they can get the fiber completely inside the cell and they can pick up a lot of fibers...each one can pick up a lot of fibers.

But the same sized cell, if it tries to deal with something that sort of size, its reaction probably to wrap itself around one end with the nucleus pushed to one side, it is physically incapable of dealing with the whole thing.

Now, people have suggested that the breakdown enzymes, the lysosomal enzymes I was talking about, tend to be deposited around the asbestos fibers, short ones, may now be deposited around these fibers because...the long fibers...because the cell can't really tell whether they are inside or out.

Because there is still a hole to the outside, then these dangerous chemicals can now leak out past the fiber that's protruding from the cell. That is one hypothesis that has been suggested.

I am not too happy with it because I don't think we've got any evidence that these lysosomal enzymes in cells are

THE WITNESS: (cont'd.) carcinogenic, able to produce tumors.

Now, it's something that possibly occur. There may well be a leaking effect of the long fibers. Apart from that, I think we've just got the facts that all the fibers are the most carcinogenic and as I said at the beginning, chemically we just do not know why.

DR. UFFEN: Just to see if we can clarify this bit about in the beginning, the chemical input, we were talking about magnesium a minute ago and we were having a little difficulty because all of them have magnesium. The difference between the amphiboles and the chrysotile is primarily based on iron or calcium or sodium. Two of us got lost when you were talking about the stability in terms of the magnesium content.

Could you back up and have another go at that?

THE WITNESS: This is where I get lost, not being enough of a chemist. I think it's true to say that it has been shown that whereas the magnesium in chrysotile can readily be removed, certainly by acids and to some extent by water or certain physiological fluids of the sort you would find in the lung, it is not possible to remove the magnesium from the amphibole in the same way.

I believe one of the main industrial advantages of the amphiboles is that they are mostly acid-resistant, whereas chrysotile isn't. This is really indicating the point that the acid can't pull the magnesium out of the amphibole fibers.

Well, chemical reasons for this, I'm sorry, I'm not enough of a chemist.

DR. UFFEN: It's rather odd that in nature when you find the actual fibers themselves in the rocks, these rocks are millions of years old. They are not what you would call unstable in their natural environment, and by and large in the

DR. UFFEN: (cont'd.) natural glass formed in nature the ones with more sodium and calcium and potassium are the most stable, and the ones with a lot more iron and magnesium are the unstable.

But it takes enormous changes in temperature to affect the stability of natural glass in nature, and when we start to talk about the small changes that can take place inside a human being or an animal, there doesn't seem to be any comparison.

THE WITNESS: You know, I'm wondering if in the rock condition whether the asbestos, the veins of asbestos ore, the fibers are so packed together that I have always imagined they were almost hidden away from any sort of chemical reaction after their formation...until man comes along and rips them out and does things with them.

I don't know if that's a fair comment or not.

DR. UFFEN: Well, I think it's not in the sense that it's a matter of time. If you have enough time, the chemical reactions take place in the rocks. But you need thousands and thousands of years to accomplish what apparently can happen in a very short time in other circumstances.

THE WITNESS: I'm sorry my knowledge on that aspect is small.

DR. UFFEN: I guess you can see what's behind our questions about the chemical nature of this. If we can get this thing resolved from the point of view of our Commission, it has implications in so many different areas of whether or not the chemistry is triggering or ineffectual, or is there any hope for treatment. If there is hope for what to do in the future and we spend all our time on physical dimensions only to discover ten years from now that it was triggered chemically, it would be a terrible waste of time.

THE WITNESS: Indeed, yes.

THE WITNESS: (cont'd.) I think I indicated there is no real evidence that chemistry comes into play. The statement that I made, that you drew my attention to, was merely a loose way of indicating that there was a difference between different asbestos types. To that extent I'm simply turning to chemistry.

One's ideas change very rapidly with new experimental data. I would now put much more emphasis on breakup, which probably is related to chemistry but is not chemistry in itself, as the important factor.

Now, so much of what I'm saying is some concrete experimental evidence and ideas developing from that, and of course what we really need is more evidence to substantiate the ideas.

I think I have mentioned before, I think some of our most important fields of research in the future should be this breakup or lack of it. It might be an idea that can be proved to be wrong, but so much of the evidence is in favor of it at the moment that I think we can demonstrate actual breakup and we need to study it in different conditions to decide whether the idea really is true, given long enough, that things like chrysotile will break up and go...therefore to man relatively safe...whereas in short-lived species they haven't got time to break up and go before the proper amount of time.

I think we do need a lot more information on it.

DR. DUPRE: Is there a way that you could just help a layman here in terms of explaining what you mean when you make the statement that fiber breakup is related to chemistry but is not the chemistry in itself?

THE WITNESS: The onus is a matter of word useage. Probably what I mean is, certainly there is evidence that different types of asbestos break up at different rates.

Since the different types of asbestos have different

THE WITNESS: (cont'd.) chemistry, to that extent you could say that fiber breakup relates to chemistry or occurs with different chemistry. But it may not necessarily depend on the chemistry.

If one says that chrysotile breaks up faster than amosite, it may be the binding of the fibrils which is not too much to do with the different chemical structure of the asbestos fibers.

This is hypothesis or suggestion. It's very difficult to be sure that it's not chemistry. One can say there is evidence of difference in breakup for different types of asbestos and different types of asbestos do have different chemistries.

I was going on to one more aspect.

DR. DUPRE: Is this the Cairo...?

THE WITNESS: The wet dispersed chrysotile study was the one I presented at Cairo, yes. It will be out when the Conference report appears, which may well be another year the way conference reports go.

We are, in fact, continuing work looking at some different varieties of wet dispersed chrysotile, and the results of that study will be available in another eighteen months to two years.

I simply wanted to see if we could get evidence that different types of wet dispersed chrysotile might separate at different speeds and this might relate to different (inaudible). That study is still ongoing.

Now, I think the conclusion can be drawn from the studies I have mentioned today certainly is that long fibers, long, thin ones, are more harmful than short fibers. But quite obviously a very important question indeed is are the short fibers completely innocuous or only relatively so.

THE WITNESS: (cont'd.) Our data certainly indicates you get less tumors with short fibers, but the real information is if you have asbestos of any short fiber length, do you get any tumors at all.

We certainly haven't got the definite answer to this. Two workers have looked at this problem - Stanton and his group and Professor Pott in Germany - and undertaken experiments where some asbestos types were very finely ground indeed so that they have a very high proportion of short fibers or very small proportions of long fibers.

The results of these studies show much fewer tumors in each case with the short fiber samples, but in each case some tumors did develop.

Now, it has been suggested these experiments should be interpreted as suggesting that short fibers to some extent can produce tumors. But I wouldn't accept that evidence exactly at the moment, for the following reasons: I think as I have already indicated this morning the breakup of asbestos is such...the possible potential breakup of asbestos is such that you could treat a sample in a way that would increase the proportion of short fibers and actually increase the absolute number of long fibers.

Does that need spelling out, or has that been obvious from what I've been saying?

Let me do so in case you haven't followed.

Let's imagine you've got a dust cloud, a hypothetical one that we would love to have, a hundred percent long fibers. A hundred percent of fibers at say, ten microns in length and about one point five microns in diameter. In other words, Stanton's highly-carcinogenic size.

Now, because these bundles consist of so many individual fibrils, magnified, you can see how the fibrils are packed together in a big bundle, and the one point five diameter

THE WITNESS: (cont'd.) fiber, you would have something in the order of one thousand individual fibrils.

Let's take one of the fibers in our one hundred percent long-fiber cloud and split it up into a thousand individual fibrils, all of them ten microns long. Out of that thousand let us take nine hundred and ninety of them, leaving ten aside.

The nine hundred and ninety, let's chop up into one-micron lengths so that you get ten short fibers. That means in your final cloud you will have nine thousand, nine hundred short fibers and ten long ones.

Now that in fact is ninety-nine point nine percent short fiber, but instead of your one original long fiber you have now got ten.

So simply grinding up your asbestos, increasing the percentage of short fiber, isn't a complete guarantee...until you are sure there's nothing long at all...that any reaction you get is entirely due to short fibers.

I think one should remember this caveat.

We are in the middle of a study that may prove interesting. We've got from Johns-Manville in the United States what I think is probably the best short-fiber sample of asbestos ever produced. They've taken a lot of trouble over it.

We were originally told there would be nothing over five microns in it, which would make it marvellous. In fact we found very few fibers over five, and we rather hope that there is nothing over ten which would mean it's certainly the best short-fiber sample anybody's ever had.

DR. UFFEN: Can you put a test to this by, after the animal is dead, taking some of the tissue and examining it to see whether there are...what is the distribution of fibers in the actual animal that you are observing?

THE WITNESS: We would very much like to do this,

THE WITNESS: (cont'd.) and we've tried it. But we are not happy with the results we have got for the simple reason that we found it can be demonstrated the very process of getting the fiber out is such that it can break up a lot of the fibers that are there, and at the moment we are not happy that we've got a technique that will get the fiber out in the same fiber length that it's sitting there in the first place.

When we have, undoubtedly this is a most important study. At the moment I would suspect anything that we got would have an exaggerated portion of short fibers because we would be breaking up a lot of fibers in getting them out and we haven't got any easy answer to this problem at the moment.

I think that almost concludes what I wanted to say this morning. I was just saying we are doing some work on the Johns-Manville sample. We are comparing the short-fiber sample to a long-fiber preparation, amosite from the same bag. We have simply generated a dust cloud, and in fact it's a very long-fiber cloud with a higher proportion of long fibers than any other one we've seen, so we will have an answer soon.

If, by chance, that short-fiber cloud produces nothing, then I think we will have good evidence that short fibers are completely safe.

If it produces a few tumors, then we are back where Pott and Stanton were - is it the very few fibers over five microns - and then we've got to look for a better cloud, perhaps with nothing over five microns.

We are left on this subject of what are the important factors in tumor production from asbestos, with the idea that it is probably the number of long, thin fibers actually within the lung tissue that is the important factor. Added to which they've got to stay there for the length of time a particular species needs to produce a tumor, and there is

THE WITNESS: (cont'd.) obviously so much more information we need, and at the present we simply haven't got it.

DR. UFFEN: At coffee break you made a very interesting observation when we were just chatting, and I wondered whether you would just like to repeat it briefly, and that was whether or not it's important whether the fibers get into the nucleus of a cell or in the..what do you call it...

THE WITNESS: The cytoplasm.

DR. UFFEN: The cytoplasm. And you mentioned something that I had not ever heard before about the importance of the cytoplasm.

THE WITNESS: Well, I think what we were discussing was the fact that it's exceptionally rare, if it appears at all, for fibers to be found in the cell nucleus. Obviously the cytoplasm is the area where the fiber is first taken up.

I can't remember ever seeing an example of a cell with a fiber within the nucleus. I can imagine mechanically it could happen, cell movement might almost impale the nucleus on the fiber, but I would suspect that could be a lethal happening and the cell would rapidly die and it would be impossible to obtain pictures of it.

That's my experience. It could happen, but it must be incredibly rare because I have never seen it.

DR. UFFEN: Then the conclusion is, is it that whatever message gets to a cell and turns it into a cancerous malignant thing comes through a message in the outer part of the cell, not through the nucleus? In other words, we are affecting the DNA message in the cytoplasm?

THE WITNESS: I think that is true and I think we are more and more beginning to understand in the field of cell biology that in the complex organism, made up of many, many cells, one of the most important control systems exists on

THE WITNESS: (cont'd.) the cell surface where it touches the next wall cell, and you certainly get a lot of messages passed from cell to cell and a lot of messages passed from the cell surface into the interior. I think a lot of people would be happy to suggest at the moment that the control mechanism, the normal one which tells the cell to divide, could well come from the outside, work through into the nucleus, switch on the nucleus as required, and in normal tissue turning off again.

If that's so, the carcinogenic stimulus could come in the same way.

DR. UFFEN: Would I be right in saying that I'm not likely to read that in elementary biology books?

THE WITNESS: It's probably true, but I think that can certainly be accepted from molecular biologists these days as being a likely generalization, and they are busily looking for the details of exactly which protein molecule is involved in the control.

DR. MUSTARD: John, could I just ask a couple of questions?

MR. LASKIN: Sure.

DR. MUSTARD: You are not proposing that the monocytes become the malignant cells, are you? You are proposing really it's the other cells, the cells lining the lungs, the cells lining the respiratory tract?

THE WITNESS: We are dealing with two types of malignancies, two general types of malignancy, but both are carcinoma, where quite obviously the malignant cells are the ones lining the respiratory tract. They are the ones that produce tumors in cigarette smokers. The histology of the tumors is similar. Some people say with asbestos you get more of one particular type than in cigarette smoking, but by and large we are dealing with the same family of tumors.

THE WITNESS: (cont'd.) The mesothelioma is a much stranger tumor, and I'm not too sure anybody knows all aspects of it. It's strange because it's a tumor of the next epithelial type of connective tissues.

Certainly the early stages of mesothelioma production in rats, where we have done some electron microscopy, I can't tell the difference between what are obviously early tumor cells, because you've got a mass growing, and cells you find in the asbestos granuloma....rather like macrophages except that they haven't got any asbestos dust in them.

So what is the cell involved in the rat or the human being? From a mesothelioma point of view, again one might... it might be helpful to summarize; the surface of the body cavities is covered by a single layer of cells that flatten themselves out very much like fried eggs, so that a series of them edge-to-edge covers a surface, with the cell nucleus forming the yolk of the egg.

Now, I think initially it was certainly felt that it was these cells, which are called mesothelial cells and are normal, turn into tumors producing mesothelioma.

I am not convinced of that myself at the moment. Mesothelioma has a mixture of epithelial-type cells which could come from this or connective tissue-type of cells which are difficult or impossible to distinguish from other types of connective tissue malignancy.

In the early rat stages, I've got a feeling we've got a cell which is multi-potential to the degree that it can either become a flattened cell or it can produce something that is akin to a fibroblast.

DR. MUSTARD: I guess really the question I was trying to get at is, the theory that you've got on the board is in effect that the monocyte is unlikely to become the malignant cell and that it's really products either released from the

DR. MUSTARD: (cont'd.) monocyte during its partial phagocytosis or incomplete phagocytosis of a fiber, or products that are released and lost when it dies, and that presumably those products either have to be taken up by your cells that undergo transformation, or affect the surface of your cells that are going to undergo transformation.

THE WITNESS: You've picked out an obvious, very obvious and very important point, and I'm not sure of the answer.

Certainly in the asbestos granulomas the local experience will eventually produce mesotheliomas. We've got cells that contain asbestos, but apart from that look very much like the early tumor cells.

So I wouldn't rule out the idea that carcinogenesis occurs because...mesotheliomas occur because some of these multipotential cells pick up asbestos.

I think that's different from talking about the really obviously committed macrophage, which I think is probably an end cell who does nothing else.

I think there are other multipotential cells which may multiply under the stimulus of asbestos in the lungs. They may pick up asbestos and may be pushed into tumor production by this.

The alternatives are a series of hypotheses by which the asbestos is in the macrophage and somehow that fact affects cells around and makes them become tumor cells. We haven't got the answer. It could be so. It could be so.

MR. LASKIN: Can we break for lunch.

DR. DUPRE: Is this an appropriate time, counsel?

MR. LASKIN: I think it is, Mr. Chairman.

DR. DUPRE: To rise for lunch?

THE WITNESS: I have reached the end of what I

THE WITNESS: (cont'd.) wanted to say.

I'm simply very pleased to deal with questions as they arrive.

DR. DUPRE: That's very kind of you, Dr. Davis, and may I take it then that we will resume at quarter past two?

MR. LASKIN: Quarter past two.

DR. DUPRE: Quarter past two, then.

THE INQUIRY RECESSED

- - - - - - - - - - - - - -

THE INQUIRY RESUMED

DR. DUPRE: Dr. Davis, are you ready?

THE WITNESS: Yes, indeed.

DR. DUPRE: Indeed.

Counsel, will you proceed, please?

MR. LASKIN: Sure.

MR. LASKIN: Q. I just have a few questions on this issue of fiber size distribution before we leave it, Dr. Davis.

Do I take it that the Stanton research that you told us about this morning is consistent with the results of your own research at Edinburgh?

THE WITNESS: A. As far as we can determine, yes. We wouldn't, from our data, be able to put a specific length on the most dangerous type of fiber.

Now, as I indicated this morning, we've now got what I think is quite good evidence that the very, very finest ones are the most dangerous. But we certainly agree that long, very thin fibers are the most dangerous ones.

Q. When you say the most dangerous, are we talking about carcinogenic potential and fibrogenic potential, or are we just talking about the ability to produce cancer?

A. In most cases, fibrogenicity and carcinogenicity

A. (cont'd.) seem to go in parallel. You do get some exceptions, but saying the most dangerous fibers I was indicating in general both fibrogenicity and carcinogenicity.

Q. When you talk about carcinogenicity, you were talking about both lung cancer and mesothelioma?

A. Yes. As far as inhalation studies are concerned, experimental animals have produced quite large numbers of bronchial carcinomas, very few mesotheliomas - which is probably the human situation after all - so that if we come into statistics on mesothelioma, we probably haven't enough number, sheer numbers, to do very much.

For mesothelioma production we tend to rely more on the injection studies, which are unnatural - but unnatural in being unduly sensitive, producing an unduly large number of tumors.

Q. Is there anything which you are aware of in the human studies, either in looking at lung tissues afterwards or in any of the other studies, which either supports or detracts from what apparently your group and Stanton have found with respect to animals and long fibers?

A. I don't know of any such information.

Q. One of the...and I here ran into some difficulty as to whether anybody put forward any evidence for it... but one of the speculations that has come across our Commission over the past summer is the possible concern that mesotheliomas may be caused by the short, thin fibers. I suppose my question to you is, is there any evidence anywhere that lends any support to that proposition?

A. Well, I dealt a little bit with that subject before lunch, saying that there are some animal studies where finely-ground asbestos has been shown to produce a few mesotheliomas. But I did point out that even in these samples

A. (cont'd.) certainly you would have had quite large numbers, although a tiny percentage, of long fibers. But we still can't be sure whether it's the short fibers or the tiny percentage of long fibers that are causing the trouble.

I think one of the pieces of information which has worried people, and I think it certainly needs to be confirmed or refuted, is the finding by the French group - especially LeBouffant - where he was examining dust from human lungs and the main finding, of course, was the one I indicated - very little chrysotile in the lung tissue, relatively large amounts of amphibole, although the exposure data seem to indicate the opposite.

But LeBouffant's surprising statement was that when it came out to the pleura where mesotheliomas develop, all he could find was firstly chrysotile, and secondly, very short lengths of chrysotile.

Now that, I think, is a very, very surprising finding. It has not yet been confirmed by anybody, but I think that perhaps is one that has led to perhaps more speculation on the danger of short fibers than there would otherwise have been.

I would perhaps like to speculate myself that if LeBouffant's actual statement is true, that maybe what is happening is that he got a lot of...or the cases involved might well have had long-fiber chrysotile in this position previously and it broke up, as we have discussed.

Now, whether that means it was in a position to produce tumors, whether it lasted long enough to produce tumors, whether it actually ever did, is something that we really can't speculate about.

But I think it's most important to check that statement and find, if everybody agrees, that really short-fiber

A. (cont'd.) chrysotile is what you mainly find out in the sensitive mesothelial area.

DR. DUPRE: Dr. Davis, could you repeat the name of the expert?

THE WITNESS: This is LeBouffant, Viron (phonetic) LeBouffant from Serche.

DR. DUPRE: That's spelled?

THE WITNESS: The name? B O U F F A N T, LeBouffant.

DR. DUPRE: LeBouffant.

THE WITNESS: I forget exactly where the presentation was published, but it will be mentioned in that review article. Which one will that...?

MR. LASKIN: Tab thirteen.

THE WITNESS: It's that one as well. That's it. The French groups work very closely together and LeBouffant made the statement elsewhere and Sebastien's group has tied in with it.

Which number did you say?

MR. LASKIN: Tab thirteen, Dr. Davis.

DR. MUSTARD: Is the Sebastien group's work confirmatory of the other work, or is that just really the same work?

THE WITNESS: They work so closely together that honestly I'm not sure of the answer to that.

They work very, very closely together indeed.

The article I was talking about was one produced last year on the Relative Effects of Asbestos. It was that largish, red document. I'm not sure which number it will be on this ...

The reason I mention is that I will have the reference in here. LeBouffant (title of article in French) Review Francaise de Maladie de Respiratoir, 1976, was the reference.

MR. LASKIN: Q. To your knowledge does he himself offer any explanation for what he says he found?

THE WITNESS: A. As far as the finding of short fiber only out near the pleura, he hasn't really got an explanation. As far as finding very little chrysotile in the main lung tissue is concerned, his suggestion is the one I have already indicated. He seems happy with the idea that the chrysotile breaks up and is removed more easily than what is probably the relatively-small proportion of amphibole that people inhale.

Q. So do I take from what you are saying if one were to accept his findings on their face that one possible explanation would be that it was the long fibers that were there on the pleura and may well have caused the mesothelioma, and then have started to break up when he looked at them?

A. This is a possibility I would suggest, certainly.

Q. Is another possibility that this breakup factor could have taken place elsewhere within the body and then could have these now-shorter fibers then found their way to the pleura and remained there?

A. There is again the possibility of this, because short fibers certainly would be transported more easily. Dust transported out to the pleura probably goes inside macrophages, to a large extent. But he would have imagined some of it would be relatively long.

But it is possible that only the relatively short stuff gets moved that far. Certainly we are left with the real question that here is a definite statement that could indicate that short fibers are harmful , and it's most important we check up on this.

Q. How do you do it? Is there any test or any experiment you can do that will...?

A. I think the first stage is that a number of groups, working completely separately - we have this additional French reference that I'm not sure is entirely independent - but if a number of groups come up with the same basic observation that they are only finding very short fibers of chrysotile in this area, then we'll know that the initial fact and observation is correct.

Then, of course, we must explore further to prove to ourselves whether or not these are actually dangerous fibers. If you ask me how to do that, then the only way and one that we've failed so far, for the reasons that I've mentioned, is to get a sample of dust with only short fibers. Once we could obtain that sample, then simple experiments of injection and inhalation would show whether or not the fibers could be dangerous.

But up to now, no sample produced has had nothing below five microns.

As I indicated, I think we've got about the best sample so far, although still an odd fiber just over five microns.

Otherwise, I can't think of a way of exploring this from an experimental point of view.

Q. Because clearly this has significant implications for how you define a fiber for regulatory purposes and I note in one of your articles, in fact the one in the British Journal of Cancer at tab ten, you offered the suggestion that perhaps we should keep the five micron lower limit for defining a fiber, but in addition should take another count of fibers greater than twenty microns in length.

Is that something that you still subscribe to or would propose?

A. I would, and for the reason that although we are not quite sure that this would produce some very useful information which may or may not correlate, if the Stanton idea

A. (cont'd.) of long, thin fibers really is true, he really said fibers over eight microns. But certainly there would be the indication, and many people have said, it's the fibers that are too big to phagocytoze, which means certainly that fibers over twenty would be expected to be really nasty.

Then it's a matter of seeing whether or not the number of these fibers in a factory dust cloud is what we really need to know.

You see, I think most people would agree that the five micron limit for factory dust counting was an arbitrary one pulled out of a hat. It seemed logical at the time.

Now, already from Stanton's information fibers five or six microns are below the figure he suggests is anywhere near the worst, so that if you had a factory count you might have a fantastic number of six-micron fibers, but nothing over twenty or nothing over ten. Let's put it that way.

But your count would be exceedingly high.

On the other hand, you might have a factory count with much lower number over five microns, but most of them might be over ten or over twenty. If that were the case, and the suggestions I made from Stanton's work were true, then it would really be...the count we really want to know are those in the dangerous range - the plus-ten, possibly plus-twenty fiber size.

Now, the only way we can get this sort of information is, I think, to start counting in the factory in this way. It would, of course, mean a lot of extra work for the counters and obviously wouldn't immediately be fitted in as the usual routine.

But I think people doing factory counts, it would be very useful if they could fit in every factory some counts...the routine fibers-over-five-microns, and then the fibers over twenty, some figure like that. We might well find

A. (cont'd.) that this correlates very much better with disease. It might give us a much better idea which are the dangerous clouds, the dangerous factories.

This suggestion is simply based, I think, on a logical extrapolation from Stanton's fiber dimensions.

The fact that one would not suggest simply changing your figure - instead of counting the five micron ones, count the twenty micron ones - is that you would then move away from the baseline we know about.

What you need is to retain your present baseline and build some new information on top of it.

Q. Until you can use it.

A. Which unfortunately means double counting, at least on some occasions.

Q. While we are on the subject of factory counts, could I just explore with you for a moment the difference, if any, between the kind of factory size distributions you get and the kind of size distributions that apparently are produced by the UICC standard reference sample fiber types?

A. We've got some information on this. I think a simple general statement would be that the UICC reference samples, we realize in retrospect, were too-finely ground, so that their overall fiber-length distribution is a bit on the short side of a lot of factory dust samples.

We know this from a lot of the simple factory counting information that we've got, where we have in the Institute done differential counts. We have had preliminary looks at fiber-length distribution in the counts and certainly a lot of them have shown that the average fiber length is away above the corresponding UICC.

But it does tend, I'm sure, to vary in the factory, depending on which process you are using. We did undertake one

A. (cont'd.) inhalation study with some samples collected from the factory environment. We got a sample of chrysotile from a factory only using chrysotile, and a sample of amosite in the corresponding way.

I think it's true to say that the chrysotile sample didn't...it was a relatively short one by factory standards. It didn't differ too much from the UICC, although it was slightly higher.

The amosite one was considerably longer than the UICC amosite.

The results - to some extent they were what we would have expected. To some extent they were a little different.

The longer factory amosite samples certainly produced a lot more fibrosis than the UICC amosite. We were rather surprised to find that even this sample didn't produce many tumors. In fact, I don't think it produced any, and I'm not quite sure of the explanation for this.

I think your question is really relating to factory samples in general, and the general statement would be that they would tend to be longer than UICC samples.

Q. One of the things that I thought I got out of reading your articles was that when you are talking about the UICC samples, it would appear that percentagewise there were more...that the chrysotile fibers tended to be longer than the amphibole fibers.

A. In our inhalation cloud, yes. Longer than UICC amosite or crocidolite.

Q. Which then would be consistent with one of the propositions you advanced earlier for trying to reconcile the apparently divergent results between human studies and animal experiments?

A. That is right. We suggested that in the

A. (cont'd.) 1978 paper. I think I indicated this morning that I still think this is partly true, perhaps largely true, but now I think I would like to consider the additional factor that these fibers...that there were more longer fibers to start with, but chrysotile probably has a greater potential to break up into even more fibers in this range. So we may have the two factors working together there.

Q. When you started off that subject about putting together the animal experiments and human studies, you made the statement about the acceptance from the human studies point of view that crocidolite appeared to be the most dangerous.

Can I just understand, you based that judgement on its effects in causing mesothelioma? Or do you extend the statement to it being relatively more dangerous than the other fibers in terms of its causing lung cancer as well?

A. I think the only really important data relates to mesothelioma, and here one would pick up the obvious groups of people - those studied by Chris Wagner in South Africa and the gas mask workers studied by Steven Jones or Corbett McDonald over here as well.

Hans Weill, of course, recently has published some information, epidemiological studies, where there was a suggestion - he had groups of workers in factories, some had been exposed only to chrysotile, some had had a little bit of crocidolite, and he suggested that the crocidolite-plus-chrysotile group had a rather worse record, including tumor production, than standard chrysotile, pure chrysotile ones.

I think he would admit that although this is a logical suggestion, the data was by no means conclusive. So that in answer to your question, I would feel that the evidence that crocidolite is more nasty to human beings than the others really does depend on mesothelioma production rather than, certainly, asbestosis, where I would suggest there is no evidence at all

A. (cont'd.) available, or bronchial carcinoma where the evidence is, I think, very poor.

Q. Looking at the human evidence, where does amosite fit in in all of this?

A. That, I think, is a very difficult one. As you know, there has been a suggestion recently...and I think Britain has followed it...in suggesting that although amosite is not as bad as crocidolite, it could be considered worse than chrysotile.

I'm not too happy with this interpretation of results. Perhaps I'm being biased a bit by animal studies there, but looking at the human evidence pure amosite exposure, I think the best-known group of people were Selikoff's group, and he certainly showed that amosite was a dangerous material.

But for myself, I don't think he was able clearly to demonstrate it was worse than chrysotile with similar exposures. I don't think he had that information.

So that as far as amosite versus chrysotile, or amosite versus crocidolite, is concerned, I don't think we have really clear human information. We haven't the information that it's highly likely to produce mesotheliomas, though we know it can.

Chrysotile can produce mesotheliomas. It seems to be crocidolite in humans probably produces them more easily.

But I don't think we have really definite evidence that amosite should be considered worse than chrysotile. That's just a personal opinion.

Q. I take it from what you said this morning that as far as the animal studies are concerned, amosite, if anything, appears to come out the best?

A. That would be a true interpretation. If you look at the inhalation studies that our group and Chris

A. (cont'd.) Wagner's group did, you will find amosite tends to produce fewer tumors.

Injected, after injection studies we tend to get fewer tumors with amosite, and they take longer to develop.

As we've said this morning, there may be a breakup factor, a rat-lifespan factor, which might eliminate chrysotile...but shouldn't eliminate the difference between crocidolite and amosite, and if it doesn't, then the figures really would suggest that amosite is very, very much better than crocidolite in mesothelioma production.

Q. Is there any speculation or hypothesis as to why that might be?

A. There is one. It's simply that the amosite fibers tend to be bigger, certainly than crocidolite. By bigger probably meaning they have a larger diameter.

It's reasonably logical to suggest that the proportion, the total number of fibers within Stanton's critical thin size dimension may be smaller with amosite, significantly smaller than with crocidolite.

Crocidolite fibers can be about the size of chrysotile - very, very thin. And yet such evidence as we have is that they are pretty tough and probably don't break up nearly as easily as chrysotile.

Q. Does amosite have that breakup phenomenon at all?

A. We really haven't got the data. As I indicated this morning, this is where we do need to do a lot more studies. Undoubtedly amosite can break up to a certain extent, but if you are asking a specific question - have we any details of the relevant speed of breakup - the answer at the moment is no.

MR. LASKIN: Dr. Uffen has a question.

DR. UFFEN: I think it's appropriate here, I'm not sure.

DR. UFFEN: (cont'd.) All your measurements have been done with gravimetric...not all, but the one that a lot of them are quoting...at the same time as in industry the membrane filter method is being used, giving the results in the numbers of fibers.

Is there a possibility that some of the conclusions are affected by how you go from nanograms per cubic meters to numbers of fibers per cubic meter?

THE WITNESS: I think the answer is that in all our studies we have done both.

DR. UFFEN: You have done both?

THE WITNESS: Mmm-hmm. Certainly in the paper I outlined this morning in some detail, we looked at both the mass and the number of fibers. And even in other studies where we are not doing comparisons but looking at a particular dust, we would choose a mass dose because this is relatively easy to control and we can make sure the mass remains the same day after day after day.

We would take rather a fewer number of random samples where we would do fiber counts, so that at the end we would give, we would say the mass dose was ten milligrams, the average fiber number was so many per cubic centimeter of air, and that would be given in all publications.

It varies tremendously...

DR. UFFEN: It does vary tremendously?

THE WITNESS: The UICC chrysotile figure for a ten-milligram cloud greater than five microns is about two thousand fibers per ML, whereas the wet dispersed chrysotile we were talking about this morning is down to one hundred fibers per ML.

There is a tremendous variation, but at least we do record it.

And then we've got the additional factor. Those fiber counts are done in the same way as the factory, with the light microscope, because we wanted that sort of comparison.

THE WITNESS: (cont'd.) Doing the counts with a scanning electron microscope, we can see finer fibers and you get a completely different picture...actually much higher.

Doing the count, if you can possibly spare the time, with a transmission electron microscope, by which you can use any magnification but which takes an immense amount of time, you would get a completely different figure - very, very much higher.

DR. UFFEN: You tend to give your results in the gravimetric method. You seem to do it more often that way.

THE WITNESS: Well, perhaps we highlight this, but I think you will find in all the publications - I hope so - that we have mentioned the fiber number as well.

DR. UFFEN: I'll come back...it may be in there, but I just didn't find it.

One more related question: When you are dealing with animal tissue or animals, is it better to use the gravimetric method than fiber counts?

THE WITNESS: You mean when you are examining the amount of dust that you've got into the...

DR. UFFEN: If you expose a rat to inhalation and then you later on cut him up and have a look at his lungs, and so on, is it better for you to use the gravimetric measure?

THE WITNESS: For technical reasons, yes. The problem is this: We are not entirely happy that we can get dust out of the lung without further breaking up the fibers.

DR. UFFEN: Okay.

THE WITNESS: So we don't trust the count we would get at the moment, whereas the gravimetric figure won't change. At least we've got something we can trust.

We would like to get the counts, very much indeed, and we've still got a lot of work to do to satisfy ourselves we can get the dust out without changing its size and shape.

DR. UFFEN: That suggests to me that there is, in the future we would be very wise in the factory place then, to continue to use both measurement methods simultaneously so that in the future we would be able to relate the measurements with the results of animal experiments.

THE WITNESS: Can I answer that by saying, is it normal practice to do gravimetric estimations very much at the moment? I don't think...

DR. UFFEN: Well, in the Province of Quebec, they do both.

THE WITNESS: I don't think we do in Britain.

DR. UFFEN: Not in Britain, and not in the USA, but I understand in Quebec they are doing both.

DR. DUPRE: And Germany is the other jurisdiction of which I believe we are conscious that does indeed use a mass measurement as a standard. They do not rely only on fiber measurements, although they have that.

THE WITNESS: I think the problem there is...I think it's the same comparison between fiber number...the gravimetric figure in the factory is going to be very, very low compared to experimentation. But then so is the fiber number.

I would agree with you if you suggest that it's not a bad thing to have double information, but I couldn't agree that gravimetric is necessarily going to be as good or better indication of the health hazards than fiber counting.

I am assuming, of course, that by gravimetric you mean gravimetric counts of respirable dust only, because there is nonrespirable and you get a very different figure indeed, but the samplers usually allow for this.

DR. DUPRE: Could I pursue this in a slightly more specific context, Dr. Davis? Again in your tab ten paper at page 685, in your discussion that appears on that page beginning with the statement which reports the finding of your study, that in

DR. DUPRE: (cont'd.) this study the effect of fiber mass and fiber number on asbestos-related lung disease, it was clearly demonstrated that a given airborne mass of UICC Rhodesian chrysotile produced far more lung fibrosis than the same airborne weight of UICC samples of either amosite or crocidolite.

This indicates, you go on, that a single mass standard for all types of asbestos would be inappropriate.

Now, is what you are signalling to a regulator here that if he is going to regulate with reference to a mass standard, his mass standards should differentiate by asbestos type?

THE WITNESS: Yes, basically that is what one would be indicating. For the reason we have discussed, that if you fixed a constant gravimetric standard this would mean many more fibers of chrysotile than crocidolite, and many, many more than amosite.

One microgram, whatever it would be...well, in this paper if you take our standard ten milligram sample, which I remember the figures...sorry, ten milligrams of UICC chrysotile is about two thousand fibers per ML, whereas for the amphiboles you are down well below a thousand. I can't remember the exact figures offhand, but they are in this publication. We'll simply turn back and have a look at them.

MISS JOLLEY: I think they are in twenty-six, on page 454, too.

THE WITNESS: We are in a different paper there, aren't we? This is number ten. I can never find tables in my own papers, but there should be...

MR. LASKIN: What are we looking for?

THE WITNESS: Data on the actual number of fibers we found in the...

MR. LASKIN: If you look at page 797 of tab eleven, you have a table that shows numbers.

THE WITNESS: That's right. In fact, I think this information is probably included, written in the script of the

THE WITNESS: (cont'd.) previous paper.

But you can see that the fiber number for a coalston (ph.) mass is very, very different - nearly two thousand for UICC chrysotile at ten milligrams, well under a thousand for crocidolite and not much over five hundred for amosite.

So that a single mass standard certainly would be permitting very different levels of fiber number, depending on the asbestos type used.

DR. DUPRE: Let me see if I can understand the consequences of this. Is the fallout of your tab ten statement at page 685 that a mass standard for chrysotile asbestos should be a more stringent standard than the mass standard for an amphibole or for crocidolite or amosite?

THE WITNESS: If you are saying the same fiber number should be permitted for both, then the mass standard for chrysotile would have to be stricter, yes. Because there are more fibers per mass.

MR. LASKIN: Q. Just to follow that up, does the evidence support the view that a mass standard would be helpful or beneficial in assessing health effects? That's what I wasn't sure that I was getting. In other words, does it have any relevance?

THE WITNESS: My own view is that a mass standard is not terribly useful. We highlighted three different examples, the three UICC examples, because I happen to actually have figures that could be quoted. But as we've already discussed today, any asbestos that you would like to mention, treated in different ways, produced by a different machine, could produce fiber shapes significantly different. Some clouds might have more long fibers than others at exactly the same mass.

Now if we accept the evidence that we discussed this morning, that the longer fibers are more dangerous, then it

THE WITNESS: (cont'd.) is possible that a mass standard could be giving quite the wrong impression. You might easily have a mass containing very, very few long fibers, and the same mass containing a large number of long fibers, so that to my mind a fiber count gives you much better information and we did briefly discuss the idea of whether the standard count of five microns and over was still acceptable as the best possible.

I suggested there might be evidence to say that it would be very nice at least to have figures indicating the number of fibers of a longer range - whether you choose ten or twenty, probably as much of a guess as the original five, but something significantly over ten.

Q. Have there been animal experiments or studies that have tried to determine whether mass measurements for any fiber type are dose-related?

A. The paper, of course, allows that...we were discussing that a minute ago...attempting to find this, and we really find that the equal mass experiments of chrysotile, crocidolite and amosite produced completely different levels of pathology. So that we did make the statement that to that extent, within those limits, mass seemed to be completely unimportant.

DR. DUPRE: Just to make sure I understand, perhaps, your page 685 in context, and the context I am specifically interested in is the context in which a regulator should read it.

Can I take it that the message you are giving to the regulator, the would-be regulator, is that if you are going to regulate with reference to a mass standard you should beware of a single mass standard and differentiate mass standards by asbestos type?

THE WITNESS: Certainly that, yes.

DR. DUPRE: But that as a general proposition the

DR. DUPRE: (cont'd.) regulator or would-be regulator should not necessarily consider a mass standard as a useful one in regulation?

THE WITNESS: My personal opinion is that the information you'll get from mass standards could cover so many variables that it is of relatively little use. You raise the point you need a different mass standard for different asbestos types. Yes, that's a simple answer.

Effectively, you need different mass standards for different machines handling exactly the same asbestos type because they could produce dust clouds of significantly different fiber numbers...whereas the counting procedure allows for this immediately so you can see what's happening.

DR. DUPRE: So that at this point, just to make sure that my thick skull is being properly penetrated, can I take it that one of the most important messages to the regulator would be to consider the desirability and feasibility of...if he has a fiber standard, a fiber count standard...of providing a count of fibers in excess, let us say, of twenty microns in addition to the total fiber count of fibers longer than five?

THE WITNESS: This has been my suggestion, and I think that evidence has been discussed that it might be very dangerous, that it might be the ones twenty or more that are the ones you ought to be considering.

DR. DUPRE: I realize that your own expertise is not entirely into the measurement area, but from your experience do you believe that providing these two counts, the total count and the count of fibers longer than say twenty microns, is within the realm of feasibility and practicability?

THE WITNESS: You mean from the point of view of the work...

DR. DUPRE: Of the counting technology and of the skill of optical microscope counting.

THE WITNESS: I think as far as ease is concerned, it is relatively easy...especially if you use the types of graticules that are in existence at the moment where around the counting area you've actually got lengths of fibers etched. I think Henry Walton in our Institute developed these graticules and we certainly use them. It makes it relatively easy to line up any fiber of doubtful length. We do it routinely for anything over five microns. The counter simply lines up the fiber against a measured size on his graticule.

I'm not sure if the graticule already includes a twenty micron figure, but it's very easy to produce it.

So to produce such a count would be no more difficult than counting at five microns. Quite naturally, two counts involve twice the work of one count, but as far as ease is concerned there shouldn't be any problem at all.

MR. LASKIN: Dr. Uffen?

DR. UFFEN: I sort of knocked you off course a bit, but may I...tell me if I've gone too far in this, but I'm puzzled about this two different methods of measurement because one of the most important figures, one that seemed very interesting to me, was the number twenty-four in here that deals with the effects of high exposure for short periods of time compared to mean exposure. That was in 1980 and you used gravimetric measurements, and it takes an outsider a long time to puzzle his way through and translate it into fiber per CC, because this is what the workman gets exposed to is a count in fibers per CC.

THE WITNESS: Well, I think I can see what you are saying. I can't remember exactly the wording of this paper all the way through. I can imagine that we probably forgot to include the fiber number here for the very simple reason that we were using UICC chrysotile and amosite.

DR. UFFEN: And amosite.

THE WITNESS: And we had already reported on the fiber number and mass, and I may simply have felt that this information was already available.

DR. UFFEN: I think it's mentioned in there, but you have to read through it very carefully to find it.

THE WITNESS: If we left it out, I do apologize and I agree that it was an omission. But these being UICC samples, they would have had the same fiber number related to mass that we already published in 1978.

DR. UFFEN: All right. I sort of backed into that particular paper and I suspect you wanted to get into it.

MR. LASKIN: I do, actually.

Can I may, if I may, ask Dr. Davis just one or two more questions about what I was just on, and then I'll come to that paper.

MR. LASKIN: Q. Let me just ask one question which I forgot to ask before. I just want to make certain I understand that in the difference between crocidolite and chrysotile in the human studies, and as I understood it you said there was a difference and we've seen it in terms of mesothelioma, there doesn't appear to be any evidence of any difference in terms of lung cancer, and perhaps asbestosis?

THE WITNESS: A. That would be my interpretation of what has been published so far. You would get other people arguing differently on that.

Q. I guess my real question is going one step further. Is there some biological explanation as to why that should be so?

A. The differences between crocidolite, chrysotile?

Q. Why should we get more mesotheliomas with crocidolite then chrysotile, but not more lung cancers?

A. This may well be a combination of things. When you talk about lung cancers on their own, I think it would be

A. (cont'd.) accepted that the most important work was published by John Knox and Richard Doll. They published two papers. The first paper was the one that showed that they had a very large excess of lung cancer in their workforce. This was a workforce that had been exposed for many years in very bad factory conditions.

In their second paper they suggested, they looked at another group that had only started work after factory conditions improved tremendously, and they suggested in this group they had no excess of bronchial carcinomas.

So what I'm leading up to is that it may be as far as bronchial carcinoma is concerned that we are dealing with very heavy dust doses, and it may be that in the good, modern factory somebody starting work now just will not be at risk from bronchial carcinoma at the sort of levels we are talking about.

At least we've got those two papers that could indicate this.

Now, there have been many suggestions that mesotheliomas may result from a sort of tiny, insignificant dose. Whereas I don't accept the extreme of this argument, it may well be that a relatively small dose can produce mesotheliomas, and we may be in a situation where a lot of our evidence on mesotheliomas depends on the fact that chrysotile can break up and be removed from the lung much more easily than the resistant crocidolite.

In the low-dose conditions you could well imagine the lung getting rid of almost all its chrysotile, getting it out of the way before it can potentially produce mesothelioma. Whereas still the relatively small amount of crocidolite, enough of it remains and stays in the appropriate area to produce the tumors.

In the very heavy conditions, bronchial carcinoma

A. (cont'd.) production, it may be that although chrysotile broke up there was so much coming in that it wasn't able to affect the issue, and that in those conditions you did get more serious bronchial carcinoma rates.

Q. When you say...I just want to explore this a little more...when you talk about more modern factory conditions and more modern exposures, have you got some figure in mind that you are talking about?

A. Well, of course, the two papers that I was mentioned were products of the Rochdale Factory and their cohort of workers. The first paper they didn't know what their dust exposure was, but they knew it had been pretty bad. The second paper they were certainly hoping that people hadn't been exposed too much above the British two fiber per ML standard, but I'm not sure if the data are quite good enough to make that assumption.

Certainly they knew the group that didn't appear to show an excess of bronchial carcinomas had had a very, very much lower exposure level...but nonetheless a factory exposure level, for a long period of time.

Q. Is there anything in the animal studies that might support Knox and Doll on whether more modern conditions will or will not produce an excess of lung cancers?

A. I think so, to the extent that you can show in experimental studies - dust administered by inhalation - that whether or not you would get an exact dose-response, that to some extent there is a dose-response, you get more tumors and increased numbers of tumors as the dust dose goes up.

There really hasn't been enough work done to explore the lower-level dose and see at which point there would be no excess at all, but we certainly know that to some extent there is a dose-response present.

M. CASGRAIN: An excess of what? I'm sorry.

THE WITNESS: Tumors - bronchial carcinomas in this case.

MR. LASKIN: Q. But in terms of your dose-response relationships are you able to say from the animal studies whether they are linear or whether they go through the zero intercept?

THE WITNESS: A. As far as inhalation studies are concerned, no. We have done some studies of varying dose levels, but data really have not been large enough to make the sort of statement you would wish.

We are in the process, in the middle of a very large injection study exploring dose-response, with the UICC asbestos samples - chrysotile, crocidolite and amosite again. Here we are running dose levels from the rather massive twenty-five milligrams that tend to produce tumors, down to a hundredth of a milligram.

This study is not complete, but the evidence so far...at least for the chrysotile...is that the results are embarrassingly linear. I say embarrassing because you don't expect really good results out of biological experiments, and so far it looks as if we may well have a no-response dose somewhere at the bottom. Although the full experiment may change this statement.

At the moment, we are not getting tumors at the lower-dose level, but at above something at the moment, I think like a milligram, from then up to twenty-five, we've already got a lot of tumors and the numbers are exactly linear.

Now, the full study will be complete in about eighteen months.

That, unfortunately, is injection, but I think biologically it might be useful information.

Q. The other comment I believe you just made was that you were rather skeptical of the observation that mesotheliomas can occur at very low doses, and I wonder if you could...if I have

Q. (cont'd.) stated it correctly, or if I haven't done I wonder if you could elaborate on that?

A. Yes. I think this concept arose from Chris Wagner's original work, and his original cohort published in 1960 included a lot of asbestos workers from the mines in South Africa, but it included people, in addition, who had merely lived in the area of the asbestos mines, some of them only for a few years while they were children and then moved away.

From that rather general piece of information we got the extremes of statement that maybe half a dozen asbestos fibers or crocidolite fibers could be enough to produce mesothelioma. In other words, very, very low doses.

Now, I think the wrong conclusion was drawn from Chris Wagner's statement that some people had only lived in the mining area, because since then Chris Wagner himself at conferences has produced pictures - not with the specific aim of illustrating this point - but one of the pictures he tends to produce to illustrate the general layout of crocidolite mines shows that in the past...not now, but in the past...they used to surface roads with crocidolite waste. He has certainly got one beautiful picture of a land rover or a jeep being driven along one of these roads, trailing a blue cloud of dust for a hundred yards behind it.

Now, some of the roads in residential areas were surfaced with this material. It was good, readily-available material. Vehicles driving along those roads, I'm sure, produced dust clouds probably as high as anybody in the mines were getting, maybe as high as anybody in factories were getting.

So I think perhaps we have exaggerated or used this data to exaggerate the idea of really miniscule doses.

The other piece of evidence that tends to be produced has been the few authenticated cases of women who, though never exposed industrially to asbestos or crocidolite very often in these cases, but whose husbands were workers,

A. (cont'd.) asbestos workers, and all the wife did was to brush her husband's overalls at night when he came home. Well, recently I know some experiments have been done on this and it has been shown that exposing overalls to asbestos clouds of the sort that might have occurred a few years ago, for some days, and then brushing them in open and closed rooms, I think the figure is people have got clouds of over two hundred fibers per ML.

So that these women were getting what we would now call incredibly high exposures.

These are just isolated examples and instances, and obviously in all cases we do not have the data. But at least there is some data that the normal asbestos worker cases of mesotheliomas, some cases certainly have pretty high exposures.

So there is really nothing, I would say, to contradict the idea that you need pretty moderate doses of asbestos to get mesothelioma.

DR. DUPRE: Dr. Davis, do you have a citation for the experiment of brushing an overall that was exposed to a very high level of asbestos, and measuring the dust cloud that you got?

THE WITNESS: I thought you were going to ask me that, and the simple answer is no, I can't remember exactly who did it. I can find this for you and post you the answer, certainly.

The experiment certainly has been done. I'm not quite certain it has been published. But I can certainly tell you who to contact. I'll see to that as soon as I get back.

X DR. DUPRE: As for the Wagner tale about the crocid lite wastes paving roads and the possible production of dust clouds by passing vehicles, is this basically just anecdotal at meetings or has Dr. Wagner ever said anything about this in writing?

THE WITNESS: I don't think he has covered this

THE WITNESS: (cont'd.) particular topic in writing, and as I say, he didn't show the photographs to illustrate this point, but I discussed it with him, having seen the photographs, and he has agreed that certainly in these areas there is every reason to believe that localized conditions could have been bad.

One of his examples of nonexposed cases, of course, were the children in these areas. He admits that some of them played in the waste asbestos dumps.

Now, as I've said, crocidolite is by far the most dusty material. There is enough crocidolite left in the waste to make it blue, that is certain, even though there is not enough to be used industrially.

You can well imagine the children running around in a hot, dry climate, tumbling over in piles of this dusty material. I think their exposure would have been what we would call relatively high.

MR. LASKIN: Q. Do you get any kinds of dose-response relationships in your animal studies, with respect to mesotheliomas?

THE WITNESS: A. In what way? Now, injection studies we have just mentioned, and I'm saying we are certainly getting a very good dose-response.

Q. That's mesothelioma as opposed to bronchial carcinomas?

A. That's mesothelioma.

Injection studies, of course, don't explore bronchial production.

In inhalation studies I think...I'm going to use the word unfortunately, which is perhaps incorrect...but you get so relatively few mesotheliomas that nobody has been able to demonstrate dose-response. But there is a dose-response involved with carcinoma production. You are getting five, ten times more bronchial carcinomas, so that the numbers mean something.

Q. Could I just ask you briefly about one other

Q. (cont'd.) fiber type, and it's not one that often gets talked about, which is tremolite. The reason I ask you about it is that we've had some studies presented to us this summer which indicate, for example, in respect of Quebec workers who have subsequently been autopsied, a lot of tremolite in their lungs and, for example, not an awful lot of chrysotile.

I'm wondering whether your group has done any work with tremolite or whether there is some association between chrysotile and tremolite that you are aware of.

A. We have just completed an inhalation study with pure tremolite. We had a little bit of experience with this...or I did in the past...when I was doing some work with Paul Gross, over ten years ago now, when he was extracting dust from lungs and I was doing some electron microscopy on the dust samples for him.

Most of the dust samples were from people with normal urban exposure because that's what we were interested in particularly, but he had a group of about a dozen asbestos workers and I produced counts for him...I forget in which paper... but it will be seen that the percentage of fibers that appeared to be chrysotile was very small. I think it was about ten percent.

He was astonished at these figures, and he said as far as we can tell these people have only been exposed to chrysotile, and yet there were a lot of very obvious amphibole fibers in their lungs and we subsequently had the fibers looked at and many of them, at least, were tremolite.

Now, from this I know people have suggested that chrysotile samples can be contaminated with tremolite. If this is true and if what we have already said today might indicate that chrysotile breaks up and is removed particularly easily, tremolite being left behind, it might constitute a hazard in its own right.

A. (cont'd.) Now, the studies we have undertaken with pure tremolite, which was a sample we got from Korea, we've completed the study, I haven't analyzed all the data and it's certainly not written up yet, but two facts emerge. One is that we use a standard ten-milligram cloud...there were a lot of fibers, I forget the exact figure, but let's say between fifteen hundred and two thousand per ML, so that it's around the chrysotile number range...looking at the lungs there was far more visibile asbestos in these rat lungs than I've ever seen before. That's a simple statement, but it's an obvious one.

We haven't yet got the gravimetric estimations of what this means in terms of weight, but certainly we have a large number of tumors. I think it will be more than chrysotile but I'm not sure of this because you can only be sure of it when you complete the serially sectioned lungs, and this hasn't been completed yet. But certainly our experiment began to show that tremolite is very nasty to rats, and may be more nasty than chrysotile and that will mean more nasty than any other asbestos type.

So if chrysotile is seriously contaminated with tremolite, and if the chrysotile is easily removed from human lungs and the tremolite remains, this may well be a factor that ought to be considered very carefully.

Q. Can I just change topics for a moment and ask you whether your own work has shed any light on the ability of asbestos to produce tumors other than lung cancer and mesothelioma?

A. In the positive sense, the answer is a simple one - no. I don't know if you are leading up to perhaps I think a reason the important negative finding that we, in conjunction with quite a number of groups throughout the world, have explored this idea that ingested asbestos might be carcinogenic.

A. (cont'd.) We undertook a study in rats. A short-term study has been published, a long-term study is being completed and the results are being published in Environmental Research, almost any issue now.

The simple result is that in our hands that our rats can eat vast amounts of asbestos, for their full lifespan, and we find no gastrointestinal tumors.

I think other studies that have already been published have come to substantially similar results, and I'm certainly waiting - I'm sure everybody in the field is waiting - for the results of the very large United States study that has been undertaken. You'll know of this one, presumably.

Q. I'm not certain we do.

A. The United States...

DR. DUPRE: Is that the Stanford Research Institute study?

THE WITNESS: I think that is right, but I do tend to mix up the American organizations. I think you are right.

MR. LASKIN: Q. Is this the drinking water study?

THE WITNESS: A. That is right. The dust is being administered by drinking water to very large numbers of rats, and I think another species - is it hamsters that are being used? I think it's hamsters.

The numbers involved are very much bigger than we or anybody else has used, and so the results are going to be very important indeed.

I have heard a few grapevine whispers that they are going to find nothing, but nothing yet has appeared in print.

Q. Yet I gather that...at least it would appear from the literature...that there are some studies, human cohort studies, which appear to show an excess of gastrointestinal cancers, and I wonder whether in light of your own findings whether there

Q. (cont'd.) is some other biological explanation as to why you might have those findings?

A. As far as gastrointestinal cancer is concerned, I think the answer is a simple no. But I remember when Irving Selikoff produced the original suggestion that he has an excess of gastrointestinal cancer, a small excess, in a cohort of workers, I think he produced this at the New York meeting in 1964, and I remember asking the question at the time, a very obvious question, had he any evidence of an excess of any other type of tumor.

He claimed he hadn't.

There I think the matter has rested, but I was very interested to hear in Cairo this summer a paper presented by a man called Goldstein. I don't know if this is fair, his fellow epidemiologist is probably hopping mad, but he has really re-analyzed everybody else's data that has been published on the subject of tumor production, cohorts, in human beings.

He was certainly making the statement at this conference - two statements - one: taken overall there was no evidence of any increase in gastrointestinal cancer, but two: there was some evidence of an increase in cancer per se, of no particular type, but an increase in overall tumor numbers, of nonmesothelioma tumors.

Now whether that paper really stands up to critical epidemiological examination, I'm not competent to answer. I don't know.

But he was certainly making that statement this summer.

DR. DUPRE: How does this author spell his name, Dr. Davis?

THE WITNESS: I think it's G O L D S T E I N, but the paper will be coming out of the Cairo Conference Report when that is available.

THE WITNESS: (contd.) Now, if he is right on this, this might tie in with the sort of data that we and others have been able to produce experimentally.

I know there is some disagreement on this, but we looked at the gastrointestinal tissue and the other tissues of animals that had ingested asbestos for their full lifespan, and quite frankly we couldn't find any asbestos.

One or two papers have claimed that you can find small amounts of asbestos, and the reason for the difference I simply can't answer.

If that were the only piece of information I might be prepared to admit that our techniques weren't too good and we couldn't find them, but in addition to looking at animals treated by ingestion, we have looked at the same battery of tissues from animals treated by inhalation and we can find what I would call plenty of asbestos scattered around the body, all around the body, after inhalation.

Now, this could be the reason for some increase at least in overall cancer incidence in asbestos workers. If you get fibers scattered, enough fibers, well the doses wouldn't be very high, but in a large population this could explain that type of result and may even explain Selikoff's original study because we have found fibers in basically gut organs from animals treated by inhalation, where we can't find them by ingestion. Maybe the fiber wandering around the body can reach the stomach or the intestines by the back route and not by the front route.

Q. Is there some biological support for the ability of asbestos fibers to move around the body? I mean, are there passageway for it to get around the body?

A. Indeed there is the system of lymphatic channels throughout the body, and this system really duplicates the blood vascular system as a method of recollecting fluid that has leaked out of the blood vessels during its normal process

A. (cont'd.) of feeding the tissues. Some of it goes straight back into the blood vessels, but other of it has to be collected in a separate system of tubules. We do know that cells containing dust can move along these channels and can be found in the cellular aggregations called lymph nodes that you happen to find at various points along the channels.

These nodes will collect dusts and you can find them very easily. For example, in our injection studies we routinely put dust into the peritoneal cavity, the abdominal, the belly cavity, and the lung has, of course, a lot of lymphatic tissue around it. After injection, we find plenty of dust in the lymph nodes attached to the lung, so that transport along the lymphatics is relatively easy, and certainly possible.

Q. In your inhalation studies using crocidolite, have you found peritoneal as opposed to pleural mesotheliomas?

A. We find so few mesotheliomas. I think it's true that we found one peritoneal mesothelioma following crocidolite inhalation. That's the only one I remember.

We used the peritoneal route for our standard injection studies because it's easier and you can spot the animals with tumors much earlier, which is better for you and better for them.

MR. LASKIN: I probably have just a few more questions and maybe we could take a short break again, Dr. Davis, a short break and I'll just review my notes. If you are content.

DR. DUPRE: Do you wish to take that break now?

MR. LASKIN: Sure.

DR. DUPRE: We'll break then, for ten minutes.

THE INQUIRY RECESSED

- - - - - - - - - - - - -

THE INQUIRY RESUMED

DR. DUPRE: Are you ready, Dr. Davis?

MR. LASKIN: Are you all set?

DR. DUPRE: Counsel, will you please proceed?

MR. LASKIN: Q. Perhaps I can turn, Dr. Davis, to your article at tab twenty-four, which Dr. Uffen referred to earlier, and let me tell you one of the problems that we've had from some of the evidence we've heard this summer, and it relates to the concern as to whether there is any different affect from intermittent high doses as opposed to a more even, long-term exposure to asbestos.

Some of our expert witnesses this summer have indicated that the elevated risk that one sees in some studies pertaining to maintenance workers or insulation workers may be explained by the fact that those workers in particular have received high doses, albeit intermittently, and at least as I read your article at tab twenty-four, at least in the animal studies you don't appear to find any difference.

THE WITNESS: A. That is a straightforward statement from the data we published. Perhaps I could take that a little further and explain the sort of dilemma we were faced with.

Q. Could you?

A. We obviously wanted to explore this very question that you've posed, the importance of very short, peak dosage. If you consider the sort of peaks you are dealing with, you've probably got something like a difference of a hundredfold. If you imagine your normal factory background, one or two fibers, your peaks can easily go up...with the amphiboles certainly... easily go up to a hundred fibers without any trouble.

When we consider this situation, we really felt that we couldn't cope with a hundredfold differential in the experimental system. The reason is that we felt we had to have a baseline where some sort of change was occurring, to compare the peak with. If we had used a realistic baseline, one or two

A. (cont'd.) fibers per ML, we are pretty certain for the short-lived species like the rat there would be nothing to see at all.

We could easily work at the top peak of a hundred fibers per ML.

On the other hand, if you raised the baseline to the level at which you would get some results in the rats, your hundredfold peak would then become impossible on the upper limit, you just couldn't get a dust cloud to that density.

So the really realistic peak differential we felt was impossible in the experimental situation, and therefore we examined the effects of the sort of peak differential that we could achieve.

Now, these of course were not very big differences. We had, in fact, merely a fivefold difference in dust between the baseline and the peak, which would have meant, if you are extrapolating to factory levels, if your baseline is one fiber your peak would have been five fibers. In factory terms, you would scarcely have called that a peak at all.

But excepting that, we felt at least it was worth doing the study, and as you will see from the presentation we used both chrysotile and amosite. We actually worked to different levels so that we could have a baseline we could work with, and we felt that we had to use the two milligram experimental baseline with chrysotile because that meant the peak would be ten milligrams and we knew we could cope with a ten-milligram dose.

If we had used ten milligrams as a baseline, as we did with the amosite, our peak would have been fifty milligrams. As I mentioned earlier today, you just cannot get a chrysotile cloud up to fifty milligrams.

Maybe we made the wrong decision, but we decided we would work at these higher levels with the amphiboles, partly

A. (cont'd.) because it was quite possible to use the higher levels of amosite, and we thought it might be interesting to see what happened at those high levels. But maybe we should have stuck to the lower ones for both of them.

You'll see from the results we obtained that we make the simple statement that we found no difference following peak dosage.

Now, this really means that there is no statistically significant difference. If you look at our figures I think you will find that the fibrosis...there was a little more fibrosis with both the peaks...but my statistician friends assure me that within the limits of the experiment, that's not meaningful and basically they were getting the same results.

Again, with tumor production, even without benefit of statistics, I think chrysotile we got two malignant tumors with the base dosing and two with the peak. You couldn't get it closer than that.

Amosite, we did actually get a couple of tumors with the peak dosing, and none with the baseline dosing.

Again, my statistician friends say that is not an important observation. You need much more differentiation than that.

So a simple statement remains that there is no statistically detectible difference, but I would point out the limitations of the study on peaks. We did not get the peak differential that theoretically would have been most interesting.

Q. One of the explanations that was offered by some of the witnesses we heard for this apparent effect, was that at peak exposures - short, sharp bursts - the lung clearance mechanism may be overwhelmed and may not be able to operate in the way that it apparently does under normal circumstances or under less severe exposures. I wonder, getting away from this particular experiment, whether any of your other animal studies

Q. (cont'd.) tell us anything about that?

A. We have published one study on short-term inhalation and dust clearance, and perhaps there is information of some importance there in that we undertook studies at different dose levels...I seem to remember the dose levels were one, five and ten milligrams...and I think it's fair to summarize the results we obtained as saying naturally with the higher dosage you got greater deposition, but scarcely more in proportion from the dose.

Then after that, the clearance seemed to be a constant proportion of whatever had got in, so that within those very limited parameters we had no evidence of an overload. But longer term I don't think we've got any information.

Q. One way or the other?

A. One way or the other.

You see again you are dealing with statistics. You will notice in our peak paper that the dust figures we give on page 278 would indicate...well, the chrysotile figures, both baseline and peak, were exceedingly close. With the amosite you might say, well, the difference between nine thousand, one hundred and eleven thousand, two hundred indicates greater retention with the peak dosing. Statisticians again say within the limits of experimental error there is no difference there - certainly not a very big difference.

DR. UFFEN: Have you finished with that paper?

MR. LASKIN: You go ahead, Dr. Uffen.

DR. UFFEN: Could I ask a question about that?

MR. LASKIN: Sure.

DR. UFFEN: Would it be right or wrong of us to draw this conclusion though, from your animal experiments in the particular paper we've talked about, any conclusions about the accummulation of fibers? Would it be safe for us to say that it amounts to the same thing for fibrosis whether you get a short dose, small dose for a longer period of time or a

DR. UFFEN: (cont'd.) high dose for a short period of time? Because if you can make that conclusion, it's suggested a precautionary move is to take the person away from exposure when they've had the allowable limit. Is that a fair conclusion?

THE WITNESS: Within the limits of the experiments that we undertook, that would be a fair conclusion. But I think I indicated that I wasn't happy that we got enough difference between our baseline and our peak to necessarily get results that are meaningful in the factory situation.

We rather hoped when we started this study that we might get some obvious indication. If we got definite increase at a fivefold peak, then quite obviously a hundredfold peak would have been a really dangerous thing.

So our data must be limited to exactly the differentials we looked at, and it would appear that within those limits there was no excessive buildup when the peak was used.

DR. UFFEN: There is another problem that we have faced several times, and that is in the implementation of standards. We might have a perfectly sound standard, whatever it is, I'll use for the moment a two fiber per CC, and you monitor it in the workplace and all the records show that that is what has been happening. But some bloke who is working in a specific area regularly gets a fifteen minute blast which is well over that.

You might draw the conclusion here that over twenty years of working he is getting exposed to the similar conditions that the men used to get exposed to years and years ago. This has all kinds of implications for compensation and things like that, whether the measurement has been made in the right place and for the right time.

THE WITNESS: Well, certainly you raise a most important point. As far as you were still referring to the individual getting a short peak burst is concerned, if the data

THE WITNESS: (cont'd.) we produced really does apply closely to humans at much higher peak differentials, then I think the assumption would be that certainly you need counts for the peak that this man is being exposed to. But if you found that peak of fifteen minutes was ten times more than the normal factory level, over the day what could this mean, that he had received perhaps twice the limit? I'm not very good at mental arithmetic. And I think the conclusions you would draw from that would be valid. In other words, he has twice the limit for one day, which probably has to be considered quite insignificant.

That would be the logic of our results, but again we really are talking about very...

DR. UFFEN: That was an interesting comment. Twice the limit for one day would be insignificant.

I think most people assume that you mustn't exceed the limit at any time, so that anything over the limit is significant.

THE WITNESS: To me, I always feel that our limits are designed on the principle of what is a safe overall average dose. Now, that leaves the question of the peak. We have been talking for the last few minutes of such evidence as we have could be taken as indicating that peaks are not more important than you could imagine simply by adding in the extra dust.

If that is true, then twice the limit for one day is equivalent to working one extra day to the end of your lifespan, probably, which wouldn't be likely to be very significant.

But this is an area where certainly we've got inadequate information regarding humans. You raised a very, very important point which I'm sure is well understood, that we tend to make factory counts at particular points and what you really want to know is what is the dust count six inches in front of the operative's nose. That can be different...as you know only too well...for each operative.

THE WITNESS: (cont'd.) So that the real answers to individual danger are only going to come from personal sampling, which makes a tremendously increased counting burden on the people involved.

That, of course, is the theoretic reliability. Your factory background simply gives you an indication of probably what your overall count is likely to produce.

MR. LASKIN: Q. I just have one or two other questions, and one I forgot to ask you before relates to, I suppose, generally asbestos carcinogenesis, and we again had one or two witnesses this summer who talked to us about initiators and promoters, and I'm not entirely certain I understood the difference and as to whether it did have any significance in relation to asbestos and its ability to cause tumors. I wonder if you have any observations?

THE WITNESS: A. I don't think we've got any definite information on this point from experimental studies. People involved in carcinogenesis like to suggest the difference in this process, the initiator is chemical or a substance, a physical phenomenon, that starts off with a normal cell and really pushes it all the way through to tumor production, whereas they distinguish promoter as being something that takes a slightly-damaged cell that something else has pushed a little way towards tumor production and finally kicks it over the edge.

Now, of course, the question has been asked with asbestos - which way does it operate? Personally, I know of no information that would indicate whether it's one or the other.

Certainly we know that asbestos, with nothing else that we can determine, will produce tumors. But you could argue that there are half-transformed cells in all old animals that don't need anything other than the aging process to produce, and add asbestos to these and they will develop into tumors in

A. (cont'd.) a significant number of cases.

But I don't think we've got definite evidence on that.

Q. I suppose the subject that was raised before in connection with the effects of smoking, is it possible to design animal studies that put in the factor of the effect of tobacco or the effect of smoking?

A. It is possible, but in practice it is exceedingly difficult and complex for the following reasons: We thought about it and we wanted to do it. Now we undertake our inhalation studies, but the rats live for a whole year inside the inhalation chambers, which are large structures about one and a half meters in diameter, one half meter cubed.

Now, we add asbestos to the air as it passes through. We could easily add tobacco smoke and it would combine with the asbestos. The only problem is, a constant stream of tobacco smoke of the sort of concentration we would need would actually contain a lethal amount of carbon monoxide gas and probably kill the rats before the end of the first day.

Now, the obvious question is, why don't human beings succumb quite so quickly? The answer, of course, is that between puffs of cigarette smoke, which do contain high levels of carbon monoxide, you take in several breaths of good, clean air which keeps you going.

But we could overcome this in experimental animals. It has been done, of course, by people who are exploring the cigarette smoke effects. What you have to do is to redesign your inhalation system and have rats breathing, rats exposed only with their noses. This means you have a central tube in which you have your cigarette smoke or indeed your asbestos-dust/air mixture, and around this tube you have a series of little chambers in which you put your rats headfirst, or only

A. (cont'd.) their nose protrudes into the danger area.

Now, because you are dealing with such a small volume of air, it's possible to control what happens to it and by a complex series of dials and pumps you can supply the animals with a couple of minutes of air containing cigarette smoke, and then the appropriate number of minutes of good, clean air, and so on and so forth.

It really is an incredibly complex and incredibily expensive system to operate, and for this reason we have not used it to explore the synergistic effects of asbestos and cigarette smoke, and to my knowledge nobody else has either.

Q. I just have one last question and it relates to your literature review article which is at tab thirteen, and it's one of the final points you make, which is on page 19, and I'll just...I can read you the sentence.

You say, having looked at all the animal evidence and looked at your in vitro studies, and having looked at the epidemiological evidence, you say, "From the point of

> view of protection of the workforce, reliable epidemiological evidence must take priority over that obtained from animal experiments".

I wonder when you made that statement whether you had in mind any epidemiological evidence which you would consider reliable?

A. No, I think that was more a philosophical statement than anything else. One is being forced to admit that there were differences, apparent differences, between information obtained from human and experimental animals.

Now, the point was this: If the epidemiological evidence, which is dealing with human beings, the species we are interested in, really is good and reliable and gives you one message, that has got to be the right message. If the animal

A. (cont'd.) results differ for any reason at all, then no doubt there is a good biological reason, but the ones you are interested in are the human ones.

The real point is, of course, is the epidemiological evidence reliable. There, of course, one has to take any particular study you are talking about, analyze it carefully in detail.

That statement was meant more as a philosophical caveat than anything else, and I think we would accept that while we've got a lot of human asbestos epidemiological evidence, some of it is none too reliable.

Q. Can I ask you, have you yourself looked at the epidemiological evidence in sufficient degree to be able to give us your own assessment as to which, if any, of the studies you would consider to be reliable?

A. The simple answer is that not being an epidemiologist I've kept out of most of the arguments. I know from the outside you can never get two epidemiologists to agree on the value of a paper. I would try and keep out of this very difficult argument myself.

I know the results as they've been published. It's easy to talk of the general conclusions that the authors have made. As to their reliability, this is a matter for other epidemiologists.

I think the best example, as you all know, is the arguments that have gone on between Professor McDonald and other epidemiologists, and he is one of the best epidemiologists in the world. But people still disagree with his papers.

MR. LASKIN: Fair enough.

Dr. Davis, thank you for being so patient with me.

Did you have a question?

DR. DUPRE: If I might, counsel, just in the same

DR. DUPRE: (cont'd.) context, as I looked at page nineteen, I bear in mind that there has been some work that, from what you were telling us this morning, you have yourself been involved in, in which, of course, human lung tissue was analyzed.

Insofar as your findings there, as I recall, that of your colleagues, the effect that chrysotile fibers tend to disappear, that is, of course, not epidemiological but human evidence that could lead to the same conclusion as the very paragraph that Mr. Laskin was pointing out to you, could it not, namely the possibility that there crocidolite is...or if not crocidolite, chrysotile is somewhat less hazardous than the other forms?

THE WITNESS: That is a possible conclusion. The evidence from quite a number of studies now, as we've said before today, tend to find much less chrysotile in human lungs, compared to amphibole, than you would expect.

That fits in with the idea that chrysotile may be removed before it can cause trouble, but it's not conclusive proof. It could have caused the trouble and then been removed. But at least we have that piece of evidence that you find less than you would expect to be there, so that it does appear to be removed faster than the amphiboles.

DR. DUPRE: And that piece of evidence, for what it's worth, if it's put up against the results of your animal experiments, would account for, I guess, at least as much as some of these epidemiological studies that epidemiologists can't agree on? Is this the quality of the lung-tissue evidence?

THE WITNESS: Certainly I think the lung tissue evidence, which is making really quite simple statments within the bounds of those limited simple statements, is very reliable. I say that because simply there are a large number of studies now saying the same thing. One wouldn't put tremendous value

THE WITNESS: (cont'd.) on any one of them. But there are certainly several publications saying the same thing - there is very little chrysotile in these human lungs and yet all our exposure evidence leads us to believe that they should have had the majority of their dust as chrysotile.

But I think that is a pretty reliable statement, but it is different from saying whether or not chrysotile is dangerous or not.

DR. DUPRE: I appreciate that, Dr. Davis.

MR. LASKIN: Dr. Davis, thank you for being so patient with me. I turn you over to my friends.

DR. DUPRE: Do I have a batting order for your friends?

M. CASGRAIN: I defer to my learned friend.

DR. DUPRE: Is it Mr. McNamee who is the lead off batter?

MR. McNAMEE: I thought I would ask one final, very penetrating question, but I think John has already covered the subject.

But I would like to thank you very much, doctor, for clearing the macrophage problem. I have talked with some of the other gentlemen beside me and we are very impressed with your lucid explanation of it and I think we are all quite pleased to understand finally what that involves. Thank you.

DR. DUPRE: Miss Jolley?

MISS JOLLEY: I just have two questions, Dr. Davis.

CROSS-EXAMINATION BY MISS JOLLEY

Q. The first one is, you have been emphasizing all afternoon the length of the fiber and the possibility of measuring fibers over twenty microns in length. It was my understanding that, before today, that perhaps the diameter was as important, if not perhaps more important, and I'm wondering why

Q. (cont'd.) you are emphasizing the twenty microns in length and why don't we also measure the diameter?

A. You are making a perfectly valid point. It's simply a matter that in talking about this it was something new in additional work for people and perhaps one didn't go into it in enough detail.

You are quite right. There wouldn't be much point in measuring twenty micron fibers if they were good, big thick ones, because Stanton's work would indicate they weren't important.

So we do need a length and diameter distinction builtin to the present system. If you are going to do an extra twenty-micron count, I don't know what you would choose as your diameter but you should choose something around the practical limits that fit in with Stanton's work.

Q. I was just wondering whether you were overemphasizing length as opposed to diameter?

A. I think the point is that we have got evidence that fibers, reasonable evidence, that fibers have got to be over a certain length. Evidence is that they have got to be relatively thin, but within that relative diameter I think we've got a lot more variation. We don't understand the full importance of this at the moment.

DR. DUPRE: Miss Jolley, if you would just permit me to interject right at this point...

MISS JOLLEY: Yes.

DR. DUPRE: Can I now ask you again, in terms of the message-to-the-regulator type of question that I've been asking, if with respect to length the message to the regulator would be to consider the advisability of measuring the fibers longer than twenty microns, is there a guideline as to the diameter of those fibers? Are we talking about longer than twenty microns but with a diameter not greater than a certain length?

THE WITNESS: This, of course, was the previous question. Part of the answer is theoretical and part of it is practical.

Yes, indeed, we should be talking about a specific diameter. Exactly what...if you take Stanton's work you might think in terms of anything - because he talks about one point five microns - let's say less than two microns. The point is that two microns of thickness, you are getting down so near the limit of resolution of the light microscope that maybe for practical purposes you ought to be thinking of say twenty and less than three. Purely for practical reasons one would like it less,but it just may not be possible with any reliability of the light microscope.

DR. DUPRE: A seven-to-one aspect ratio?

THE WITNESS: Some of my dust-counting friends might say, oh, yes, we can measure two microns very easily, and they might be right. I'm not this experienced. I know we are getting down to the danger limit of that level.

DR. DUPRE: Thank you, doctor.

Thank you, Miss Jolley. I'm sorry. I just wanted to interject there.

MISS JOLLEY: No problem.

MISS JOLLEY: Q. My second question has to do with the macrophage and the lysosome...I'm not sure if I'm pronouncing it correctly...leakage. Presumably that enzyme is destroying biological material, or can. When it leaks out into the...against the alveoli cells would it not also do damage to those cells?

THE WITNESS: A. Undoubtedly, yes. I think the idea that has been put forward on tumor production is that prolonged damage caused by these enzymes might be the carcinogenic factor.

I think my argument would be that we do know that

THE WITNESS: (cont'd.) these enzymes are liberated in other conditions...any time macrophages break up...in areas of acute information, for example, and certain in chronic information, there must be liberation of these lysosomal enzymes and probably that is responsible for quite a lot of the inflammation, pain and swelling that you get at these times.

But I don't think there's any evidence that these enzymes go beyond killing a few cells. There is no evidence that they themselves are carcinogenic.

Q. It would not account for the fibrosis, necessarily?

A. It is possible that it could account for the fibrosis. There are other ideas. These enzymes are one type of substance that could escape from the cells. People have talked about specific factors rather smaller in size.

Professor Heppleston's famous factor was supposed to be a polypeptide of only about, I think, fifteen thousand molecular weight, whereas the lysosomal enzymes are quite large protein molecules and many times that size.

This is an area where there is a lot talked about and not too much really concrete evidence.

Q. My last question was about the wet dispersal method of...with fibers. You have suggested that in fact when those fibers are separated in the lungs, they are indeed individual fibers and therefore they may be more susceptible to breaking up, and perhaps therefore we can conclude that that would make the asbestos less dangerous.

In fact, the industrial epidemiology studies done in the industrial use of chrysotile indicate that it's more dangerous than at the mining/milling level where they are untreated.

Could that theory also be used to explain the opposite?

A. I believe you are talking about at least two different things, aren't you? I think it's fair to say the difference between the mine and the factory - in both places you are normally talking about exactly the same type of asbestos. It's being handled rather differently. In the factory it's probably ripped up more finely, it's more mechanically agitated during the factory processes.

For this reason, you simply get more dust in the atmosphere than you do in the mines. But what dust you do get is of pretty similar type.

The wet dispersed chrysotile is a completely different process, but it only occurs in the factory situation and therefore any effects that wet dispersed chrysotile would have would only be on factory workers or just possibly workers using the final products. But you wouldn't have a mining comparison there at all.

Q. I guess I'm asking a question about untreated versus treated asbestos.

A. Well, the results, the experimental results, that I talked about did indicate that the wet dispersed chrysotile in rats was more dangerous than UICC chrysotile.

Now, you could say that the parent asbestos of the wet dispersed chrysotile obviously wasn't UICC chrysotile, that there could be a possible variation here. But we are covering that difficulty in a moment in a new series of experiments where we are re-examining the effects of some different wet dispersed chrysotile samples, and now we've got a built-in control of standard chrysotile from exactly the same production batch as we've used in the wet dispersed chrysotile.

We will have that comparison later on.

Q. Can I ask one final question that has occurred to me, and this is another. There is a great deal of debate about

Q. (cont'd.) the whole issue of injection studies and the usefulness of it in taking it to humans, especially over the manmade mineral fibers, and for instance in a policy about cancer, if there is no epidemiological evidence but there is injection evidence, should one consider that that was worthwhile evidence to indicate that there may well be a problem?

A. I think you should certainly accept it as meaning you should look out very carefully to see what the real situation is in the human being. We realize the injection experiments are very, very artificial and we do them for the simple reason that using the normal technique of inhalation in experimental animals, the number of mesotheliomas produced is very small. Of course that's the same situation as in the humans - the mesothelioma has always been a rare tumor.

But for this reason, because they are relatively rare following inhalation, it's almost impossible to get enough of them for accurate comparison between dust types. Therefore you've got to use an artificial, an exaggerated situation.

Now, what sort of evidence from that can you take as reliable? Well, firstly, if you got no tumors at all, because we believe the rat is rather a sensitive animal, I think I would expect to extrapolate that information directly back to human beings. A substance that did not produce mesotheliomas in rats by injection, I would say would never produce mesotheliomas in humans, and I would strongly suspect I could rely on that statement.

With glass fiber, something like that that produces mesothelioma in rats, or with the wet dispersed chrysotile that in rats seems more dangerous than standard chrysotile, we are back to this subject of how would these fibers behave in the human lungs over long periods.

Now, if they will survive, I would trust the rat data. But I would have this caveat, as I've said several times

A. (cont'd.) today, I can well imagine that given the long timespan involved in humans that a dust that is potentially dangerous can actually be removed before it does much.

That could be the answer to glass fiber. As yet we haven't got sufficient data.

MISS JOLLEY: Thank you very much, Dr. Davis.

DR. MUSTARD: Can I interject just a moment on that point?

It seems to me there is kind of a dichotomy here. The modern approaches to screening for carcinogens have adopted the policy, as far as I can tell, that you can use bacterial assays for trying to determine whether a chemical substance is a potential mutagen, and therefore possibly a carcinogen.

If it's positive in those tests, you move up to animal tests in which you feed warehouse quantities of chemicals over short periods of time to animals like rats, because of the factor of time and induction. If it's a carcinogen then, it's de facto taken by most of the proposals as being a very high risk substance for human beings.

It would seem to me that if you turn it around that maybe the biologists are being a little too protective of their work. In effect what you have is a biological model which is a very direct assay for whether or not something will induce cancer, and it seems to me that your injection experiments are strong, if not stronger than, the standard, simple bacterial assays for looking for potential carcinogens. In effect, one might want to say that that is, I think it would be fair to say, very major evidence of a high risk and therefore one should be concerned about the possibility of using anything that could get into the peritoneal or pleural area.

In other words, I'm trying to put it into the other perspective rather than just the asbestos perspective.

THE WITNESS: Well, I would agree with you entirely that taking this view that is taking the chemical carcinogens, but if you have any evidence of animal carcinogenesis you assume definitely that you have a distinct human risk.

I agree with you that it's entirely logical to step from there to accept our rat injection studies...entirely logical. Nonetheless, I can see the situation which we have already discussed where these fibers, potentially carcinogenic, in fact can escape from the human lung.

So although I've got to accept your logic entirely, I'm not quite sure that this will give us the right answer.

Maybe, of course, it doesn't always give us the right answer with chemical carcinogens. But that has been the standard practice, as you rightly point out.

DR. DUPRE: M. Casgrain?

CROSS-EXAMINATION BY M. CASGRAIN

Q. Yes. I only have a few questions, Dr. Davis, and this may not be taken as a compliment by some, but I want you to know that you are one of the few experts who I've been able to understand so well so far. I want to thank you very much for the clarity and the pedagogy, if I can use the word, in instructing me, at least.

You mentioned the experiments or the findings of LeBouffant, and in this connection you spoke about the fact that one had to look at his sort of warning seriously because, if I remember correctly, having found chrysotile in the pleura in cases of mesothelioma almost consistently, one would tend to think that this would be the cause therefore.

I think this is what I understood more or less...or at least that you should take heed.

A. I think I suggested that because of LeBouffant's findings, if they can be confirmed, then one would have to

A. (cont'd.) seriously consider whether or not the short-fiber chrysotile might not be the important factor.

I think one would have to consider it. That doesn't mean to say I would necessarily indicate that it might indeed be the dangerous material.

Q. There's something that I misunderstood, perhaps, or something that I missed. In LeBouffant's cases did he find chrysotile only in cases, in the pleura, only in cases of mesothelioma, or would you not think he would find chrysotile in any event in the pleura of people otherwise healthy?

A. He looked at pleural tissues from quite a large group, and I think I'm right in saying he had some cases where the pleura was thickened with fibrosis, no tumors, and he probably looked at even apparently normal mesothelium, and I think I'm right in saying he found these short fibers in all cases to be the predominant ones. Whereas in the center of the lung he found the chrysotile that was there was present in rather longer fiber lengths, but it was now the minority dust and most of it was amphibole.

His surprising suggestion - he did surprise, I think, most of us in this field - was that out of the pleura it was the chrysotile that was the predominant dust. That has been the surprising thing and that is why I say we do need to confirm this. It is possible he could be wrong, but it does need confirmation. It's a surprising and possibly very important suggestion.

Q. Just to be clear now, should I understand that he found...I'm suggesting to you that in effect if you take asbestos workers who have all been exposed for the same period of time to chrysotile, my suggestion was - and perhaps I'm wrong - that you would find chrysotile in all of the pleurae of the people who have been exposed, as it would normally get there.

Q. (cont'd.) So that if I say that, how can one then say that this would be evidence or should be looked at with care because perhaps this is where mesothelioma comes from, if all the workers have it and if, of all these people, they don't all have mesothelioma.

You know, supposing that say ninety percent are very healthy?

A. That is a logical statement, but it would also apply to any fiber length that happened to be present in the lung tissue, because only a few people get mesotheliomas, with any dust type.

The important thing of LeBouffant's statement was firstly that he didn't find a lot of the amphiboles, especially crocidolite, out in the pleural area where we thought they ought to be, producing these tumors. That's surprising, if it's true.

He found chrysotile, but not chrysotile in relatively long fibers. He found it in the broken-up, short fibers which most of our evidence suggested were the innocuous ones.

Those are the supposed facts. The way you go on from there is, it's pure supposition.

The obvious one is that it could be that these short fibers were the dangerous fibers, but there are many other possibilities.

Q. And broke up eventually?

A. Have broken up...no, the worrying suggestion is that they broke up before they produced a tumor. But it is equally possible that they produced a tumor while they were in the long-fiber stage and then broke up. It's certainly possible.

Q. I see. In the course of your testimony I was intrigued...perhaps I didn't follow it properly then...by a sentence that you used when you were referring to the macrophages and the effect that a longer fiber had on those macrophages

Q. (cont'd.) and affect it as it would pierce it or they were not able to properly engulf it.

You talked about something - you used the words, the process tends to progress. I noted those words. Do you recall having said that? I'm trying to get back to where I was then, because I missed you, this is where I left you.

A. That little group of words doesn't mean anything to me.

Q. Well, there was something about the fact that the process of the long fibers continuing to progress, vis a vis, I suppose, its attack on the cell.

A. Is this when I was referring, perhaps, to the fact that cells having taken up dust might and certainly could die...

Q. Mmm-hmm.

A. ...liberate the fiber, which would then be taken up by new cells, and this process would go on and on as long as the fiber continued to exist?

Q. I believe this is what you said. Now I understand.

Do you mean to say in other words that the one cell would be taken up by another cell again and again, and this is the process that you are referring to?

A. Well, not so much the cell would be taken up. If the cell died, then most of the cell is made up of protein and other biological materials that can easily be digested by other cells. This would happen quite quickly, but the cells, the surrounding cells, can't digest the asbestos. They have to phagocytoze it.

I can well imagine an intermediate stage where the fibers are liberated from the cells and lying almost free on their own again until more cells come along and pick them up.

A. (cont'd.) Certainly I believe this process could go on through several new generations of cells, and the only limiting factor would be how long the fiber lasts, whether or not it breaks up, whether or not it dissolves, whether or not the cells actually escape from the lung at any point and don't die and leave their fiber behind in the lung.

Q. Can you...are you able to give me any estimate of time when you say how many generations of cells...we are not talking, of course, of human generations...but can you give me an estimation?

A. Not an accurate one. I believe it's agreed that macrophages in life have a lifespan that is certainly only measured in a relatively few months...they are an end cell... it may be less than a few months. I'm not quite sure of all the evidence on this.

In vitro, for example, they will only last for a few days in cell culture, but I believe even in lung tissues an individual macrophage, once it has started to be a fully-formed macrophage, has a relatively short lifespan. So certainly we are talking, in a rat of two-years study, we are talking about several generations. I wouldn't like to put a number on a generation.

Q. Perhaps to be a little more specific...so that in effect if I take the one fiber which is longer than say twenty microns, this is the dangerous one, as you say. That is the one that these macrophages are tackling. What I would like to know, in the light of what you just stated, that it might be picked up again once the macrophage has died. I would like to know how long that long fiber could manage to survive as a long fiber within the lung so that it would remain causing damage, as it were, to other macrophages.

A. Well, this, of course, is the most important

A. (cont'd.) point. I haven't got a simple answer, but we have discussed today the possibility that asbestos, perhaps especially chrysotile, eventually breaks up in the lung tissue and this will be the limiting factor.

But I have indicated our data on this, certainly the timespan is almost nonexistent, certainly inadequate, and this is where we do need a lot more data.

Q. On the other hand, you have also found, and others have also found, in examining lung tissue when dealing with chrysotile fibers that normally what they found is very little fiber left and at that they were normally short fibers. Is that not correct?

A. We are talking about...switching now to the human lung situation...

Q. Yes.

A. ...where people have found relatively little chrysotile, in the lung parenchyma they have found some long fiber, but of course you don't know what the original percentage was so you don't know if it was changing, but there was a lot of... there was little chrysotile overall, but of what there was, some of it was certainly long fiber and a lot of it was short.

The really important information was LeBouffant's, out on the pleura, where it appeared there were no long fibers at all.

Q. Can we stick with the lung for a minute?

A. Mmm-hmm.

Q. So you say they found long fibers within the lung?

A. Some.

Q. Some. And were those found to be directly attributable in those cases to a fibrosis, for instance?

A. You are talking about individual fibers. Now,

A. (cont'd.) if the lung burden of the type that LeBouffant had produced...

Q. Yes?

A. ...say was ten percent chrysotile and ninety percent amosite - which is a likely combination - and there was some fibrosis, how could you be sure which produced it. This is the great difficulty.

Q. What I'm really trying to lead to is another question along with the continuing effect, if you wish, of asbestos fibers once they have been inhaled and they remain, as you say, long and therefore are not expelled by the macrophages.

I think something was stated by you as well in the course of your evidence, although I think it was another subject, talking to take the people away from exposure to asbestos. I'm really coming to that point now.

If a worker is exposed to asbestos dust in minute quantities, say, after he has been exposed to large doses, with the effect, the result that he has, perhaps, remaining in his lung some of the long fiber that we have talked about, would you say that the process that you described would continue on?

It's academic...

A. We certainly have evidence from the rat experiments that the lung fibrosis progresses after you have taken the animal out of dust exposure completely. Most of the fibrosis occurs well after the dusting has ceased. One would therefore expect a similar situation to occur in human beings, so that if somebody had had a very heavy dose for a number of years - now you say if you took him out of the dust - that wouldn't necessarily stop the progression of the disease. That's one answer.

If you are saying would it be a good idea, well it might be on the grounds that stopping him getting asbestos is a good idea anyhow. But I don't think you could say it would stop

A. (cont'd.) the development of the disease if you've got enough dust already.

Q. What I really want to know, would you please tell me now about the progression of the fibrosis in the rats. Can you give me an idea of the rate at which it progressed? Or in any event, as to the parameter that permits you to say it progressed? Because if the rats had been exposed, for instance, to very large doses, especially by injection, they would have a fairly severe fibrosis to such an extent that the lung would have very little tissue left with which to function, would it not?

A. Yes, I think that is true. The data on which I would base the statement that in animal experiments certainly the fibrotic process progressed, was that paper we have mentioned quite a few times today where we looked at the mass and fiber number of the dust, the effect of this.

That applies to a lot of our inhalation studies, and our normal procedure is to dust the animals for one year and then let them live out their full lifespan, which is a total of about three years.

Since they are about three months when we start the experiment, this means they have probably got eighteen months or so after the end of dusting.

Now, if you examine the amount of fibrosis present at the end of the dusting period, you find little, not very much.

If you examine them, some of them, six months later, you get still quite a little, but rather more.

Then if you look at the oldest animals, you find that you've probably got really quite large amounts of fibrosis.

The period when it develops rapidly seems to be rather more than six months after the end of dusting. It may well be one of these factors associated with old age, as tumor production is, in the rat. Possibly one might expect exactly the same thing

A. (cont'd.) exactly the same thing in the human being.

But certainly you can be sure that most of the fibrosis develops after the end of dust exposure, so it depends on either an early reaction to the dust or dust remaining in the lungs.

Q. That was my last question on that particular subject. At that time did you, in effect, when you made those examinations, did you check precisely what remained in the lung in terms of those long fibers?

A. We checked what remained in the lungs in terms of the mass of dust. We did discuss this point earlier and I said we would very much like to determine the fiber length of the dust that remained in the lung, but we are not yet at all happy that we can extract the dust without breaking it. We know we can get it out and weigh it, but we do think that our present techniques break up the dust quite a lot. So that we wouldn't be getting the figures that we are really after. We wouldn't know what the dust was like sitting in the lung tissue, if in extracting it you broke up a lot of the long fibers.

So at the moment all we've really got is gravimetric estimations... which show that there is quite a lot of dust that remains right up to the end of the study.

Q. Are you saying, Dr. Davis, that the fibrosis that was already in the lungs of that rat when you sacrificed it, at least that particular fibrosis...how can I say it...continued on its own without the help of any other fibers present in the lungs? In other words, did the initial fibrosis caused by what you described to us, did that continue to feed on itself, as it were? This is my question. Or did it not have to have additional asbestos?

A. Well, it obviously didn't have to have additional asbestos, because most of it occurred after we had stopped giving

A. (cont'd.) asbestos. But I think it's quite likely that it did depend on the asbestos that was already given and remained in the lung tissue.

So probably what we are saying is that fibrosis in these circumstances is a long-term procedure, and as long as the dust remains in the lung it just builds up with time.

DR. MUSTARD: Can I interpret this a bit more as well?

It seems to me from what you've said that as long as the fiber, a fiber, remains unprotected...that is, is not fully incorporated into a cell or it could be incorporated, the cell dies and it appears again...fresh macrophages will come in and interact with it?

M. CASGRAIN: And create the fibrosis.

DR. MUSTARD: What I was saying earlier today, a macrophage in other situations, such as in your arteries for the development of atherosclerosis because you have the same kind of proliferative response that forms a form of fibrosis, and we know there that the macrophages can synthesize - that is, make a small protein which it releases which will cause the cells in the vessel wall to divide, which means you have more cells, which is part of fibrosis. So one would predict on the basis of what, I think, we've heard today, that as long as the fiber can periodically become available to fresh macrophages you would receive fresh stimulation to fibrosis, which seems to be quite compatible with what you have told us...

THE WITNESS: Well, I think...

M. CASGRAIN: There is a mechanical action going on, this is really what we are saying, until such time as that particular fiber which has caused that macrophage to act in this way actually breaks up so that it is swallowed up by it, and then the process will stop. Is that not correct?

THE WITNESS: This might be logical to suggest. I don't think we've got the certain evidence.

Q. Well, I'm really saying this, doctor, because I'm thinking in terms of people who, you know, once examined...and you must have heard of cases of that nature...for say asbestosis are found in the two or three years that follow that it has not diminished, but at least had complete abated. Surely you have heard?

A. Yes, I've heard of these cases. I've not been involved with any, so...

Q. That's why I was asking those questions, the like of this sort of thing.

A. Well, the evidence from rats would tend to contradict it.

On the other hand, if we follow on from other things we've said today, we have suggested that fiber can remain in the rat lung long enough to cause a lot of fibrosis and eventually tumors. I have suggested that with chrysotile, at least, it's possible that a lot of the fiber breaks up and is removed from the lung.

If that is the case, it might well be that the human asbestosis would not progress. All I was simply saying is that in our animal experiments the facts are that it does.

Q. I see.

A. Now, if you could remove the dust from the lung, if it broke up and you got almost...or even significant clearance, a very great reduction, it might well be logical to suggest the process would, I don't think regress - you've got too much solid fibrous tissue and I would be surprised if it regressed - but certainly not progress any more.

So that again, it's most important for us to determine whether or not this dust really is breaking up.

Q. Are you aware that experiments are being or have been conducted - and I may be wrong there - about the sputum and the fact that as a result of studies on sputum one has found that indeed this process that we just described is being verified in respect of chrysotile?

A. I'm not sure of the studies you are talking about. It's well known that for years you get people coughing up asbestos fibers in their sputum. We know that there is clearance to some extent.

But that could be relatively a small percentage of the total lung burden. It might not have an effect.

What we are really interested in is if you had quite a serious load of chrysotile, over a long period of time it might - most or nearly all of it - break up and be removed.

There is some suggestion from human studies, but not enough definite information.

Q. One last question, Dr. Davis. You said that at one point you needed, of course, to have new evidence using modern technology - that is, a cleaner plant shall we say - and could you give me an idea of what you would consider as a long enough period of time to be able to come to some conclusions that would be able to justify some of the theories that have been put forward with respect to the amount of dust that may be permissible to inhale without any dangerous effects?

A. I think it's guessing to a certain extent. You might get some information of interest in as little as ten years, certainly as far as asbestosis is concerned. But I would probably have thought we were talking about twenty years, because the period of time you know you will get quite a reasonable number of tumors or carcinomas, if they are going to develop.

But if you were worried about mesotheliomas, as many workers have reported, it might be forty years needed before

A. (cont'd.) you could be sure you weren't going to have any.

It's very difficult to give...

Q. I understand. With respect to mesothelioma, I think this is quite correct. But in respect of tumors generally, whether they be cancerous or not, do you think that twenty to twenty-three years would be...

A. I would have thought twenty would give you a pretty strong indication. If you really are sure of your dust figures back as twenty years, then I think that would be most important information.

Q. Finally, I think this was my penultimate question because I have another one, but it is the last one. You testified, at least you talked about the chemical, the chemistry of the fiber, and can I understand from you that in your view it is not...of course my learned friend asked you the question about...I don't know how he used the word...the protagonist...what was it you used, John? In respect of whether one was the starter or...

MR. LASKIN: Initiator.

MR. CASGRAIN: Q. Initator or otherwise. I suppose you may have answered that question.

But my direct question to you is, do you, in your knowledge, do you know whether the chemistry itself of the fibers could be responsible for the cancer?

A. Well, we did discuss this point, and it is a little problematical what exactly you mean by chemistry.

What I meant by chemistry is the actual chemical molecules existing in the dust, and I think we've got quite a lot of evidence that this is not very important.

But when we were discussing it this morning I think I went on to say well, probably under that heading of chemistry ought to be included the factors which result in the separation of

A. (cont'd.) the fibers in breakup, and that could be important.

Q. But it wouldn't be the magnesium in the fiber, or the nickel in the fiber, or...?

A. No, but here I ought to be more of a mineralogist. The very chemical differences, I believe, would be responsible for the ease with which fibers breakup or separate.

Q. Yes. But you are not saying that it would be, for instance, the actual composition, ingredients making up the fiber?

A. I think the evidence is very strong that that is not important.

Q. Assuming that, therefore, we then conclude with you that it is really the length of the fiber that might have some effect because of the effect it makes on the cell, is that correct?

A. That is the suggestion, yes.

M. CASGRAIN: I have no other questions.

Thank you very much, Dr. Davis.

DR. DUPRE: Dr. Davis, you have been very indulgent of all of us. I think at this stage the commissioners might have a few final questions to pose, doctor.

Dr. Uffen?

DR. UFFEN: I've got just one area that relates to the interpreting of the data from animal experiments relative to humans, and it's the question of scale. Do we have to be very careful if we use a little animal like a rat, whose lungs, I guess, are of the order of a centimeter or do, and we scale up to a human where the lungs are about thirty centimeters...I was always taught, you know, that volumes go up as the cube of their length and surface area goes up as the square, and this leads me to ask, do rats breathe about the same rate as humans?

THE WITNESS: No, they breathe much faster, so the

THE WITNESS: (cont'd.) number of breaths...they take a lot of breaths at a much smaller volume, actually, in the same way that their heartbeats are very much faster.

DR. UFFEN: The lung is a sort of big sponge, isn't it? It isn't just a great barrel with a shell and an inside. But when you scale up is the surface area that's exposed to fiber, relative to the volume, different for a rat than for a human?

THE WITNESS: I think perhaps the way to answer that question is to say that the size of the airspaces, the alveoli, is not too much different in the rat and the human.

The large increase in the size of the lung is because you've got a lot more spaces.

DR. UFFEN: Are the macrophages for a rat the same as, in size, as for a human?

THE WITNESS: Very similar.

DR. UFFEN: Very similar.

THE WITNESS: Within exactly the same order of magnitude. I'm not sure if there are some detectible differences or not, but certainly we are talking about roughly the same sort of size range.

DR. UFFEN: You used...you did explain to us...the best you could do, two milligrams up to twenty or whatever it was. There's no danger that you are putting a concentration into a little rat which is out of all proportion to what we should do for a human lung to simulate a similar condition?

THE WITNESS: Well, we realize in the experimental conditions we are using vastly exaggerated doses.

DR. UFFEN: I know that, but it's the scaling up that's worrying me at the moment.

THE WITNESS: I think the answer is that the rat will be taking in, from any dust cloud you would like to put up, it will be taking in probably the same fraction compared to its body

THE WITNESS: (cont'd.) size and weight as the human being - about. Certainly in the same order of magnitude.

DR. UFFEN: Just one final one. Is there any other animal that will live a little longer than three years, maybe more expensive, which we could use to solve some of the problems - even if it takes ten or twenty years?

THE WITNESS: Well, the answer is obviously yes. The closer you get to man, the better things go. The person who has had the best experience with this is Ian Webster in South Africa, who has used baboons. He has been doing this work for a number of years.

The disadvantages, of course, are tremendous cost... to get baboons in any other country than South Africa is almost prohibitive...and relatively small numbers, because you just can't keep large numbers of baboons. You are talking about groups of ten animals, ten to twelve animals, for an experimental study.

DR. UFFEN: What about a dog? Dogs live ten years, frequently.

THE WITNESS: Yes, or another animal of that size. I think most of us would feel if you were going up to that size, we would like to go to primates.

DR. UFFEN: Okay.

THE WITNESS: Because then we know that all the processes are getting closer and closer to the human the whole time.

Now, Ian Webster's studies, what's he got...he's got obviously comparable data to humans. He's got some asbestosis, he had one pleural mesothelioma in a baboon, for example.

They are obviously reacting in the same way.

DR. UFFEN: Can you teach a baboon to smoke?

THE WITNESS: I don't know the answer to that.

DR. DUPRE: Dr. Mustard?

DR. MUSTARD: There have been smoking experiments done with other baboons, Mr. Chairman.

DR. DUPRE: Thank you, Dr. Mustard.

DR. MUSTARD: I would like to ask you some questions related to, I guess it's to a couple of your tabs. One is tab twenty where you, I think, tried to look at whether feeding asbestos fibers would lead to problems in the gastrointestinal tract. You would think...you fed the asbestos fibers in butter or margarine to the rats and didn't observe any effect, which raises an interesting question.

If those feeding experiments did not work, do you have any theories as to how asbestos might cause gastrointestinal tract tumors, and mesotheliomas in the lining of the gastrointestinal tract?

THE WITNESS: I did suggest the possibility that whereas we failed to find fibers in animals treated only by injection, that if we looked at animals treated by inhalation you could find fibers in all the body organs. It's logical to assume that these had moved around the lymphatic channels.

DR. MUSTARD: Are the fibers moving through the lymphatic channels, or are the macrophages carrying the fibers moving through the lymphatic channels?

THE WITNESS: Certainly some macrophages do go. I would not rule out the possibility that some fiber might not move on their own if they could get as far.

Let's say a macrophage died in a lymphatic channel and liberated a fiber. I don't know the answer to that one, but certainly, of course, you find in your lymph nodes dust contained in macrophages and it's logical to assume that the macrophages actually travelled with the dust.

DR. MUSTARD: Now, if that is one way in which the fibers move about in the body, is there any evidence about

DR. MUSTARD: (cont'd.) the size of the fibers that would move into that route?

THE WITNESS: Some evidence, on the simple basis that the smaller the fiber, the easier it is. Certainly most of the fibers that you find in the lymph nodes would be of a relatively short size.

Now, that's not the same as saying there wouldn't be any moderately long ones, if we are talking about ten or twelve microns. I would be fairly certain there wouldn't be any two-hundred micron ones. I don't think they could get through. But there undoubtedly will be some in the ten or twelve range.

But I think you'll get a differential if you compared lung tissue to lymph node tissue. There will be a high proportion of short fibers in the lymph nodes.

DR. MUSTARD: Has anyone, in inhalation experiments in animals, looked at the size of the fibers in the pleura? To, in a sense, contrast it with the experiments, the human studies that we were just talking about?

THE WITNESS: The simple answer is no. We haven't done so for the reasons I mentioned. We are not happy that we can get the dust out without changing the fiber size distribution.

DR. MUSTARD: You also get a problem that here is the rat lung and it's so small that the sample probably is.

THE WITNESS: That is certainly true.

DR. MUSTARD: It does raise an interesting question in my mind, the whole discussion, that the question of the shorter fibers remote from the site of inhalation might well be compatible with what we think of the biology of fiber distribution, which I guess does make one a little concerned about what the significance is of one or two reports of the short chrysotile fibers being seen in the pleura...of what significance that is.

THE WITNESS: I think because...I said this report,

THE WITNESS: (cont'd.) this information, really surprised a lot of people, and I'm sure anybody looking at dust in human lungs immediately set out to try to confirm or refute it, and so far no publication on this score appeared. But I'm sure lots of people are exploring this. I know Chris Pooley is in Cardiff. We are about to start some autopsy studies on asbestos workers, and of course this is one of our main priorities. But we have been completing a very large autopsy study on coal miners up to now, and haven't had the personnel to spare on the asbestos project.

DR. MUSTARD: A final question, in any of the animal experiments have you ever found any tumors develop in the lymphatic tissue itself?

THE WITNESS: Yes. This is difficult to interpret because lymphomas, of course, are relatively common, spontaneous lymphomas in rats, and you get a much less clear differential between treated and control animals.

It's something we haven't explored too much because probably...because we thought we knew the answers, that it was bronchial carcinoma and mesothelioma we were interested in. But certainly the simple answer to your question, we get lymphomas in the rats. We certainly get some, probably nearly the same numbers in the controls in the experimental ones. I wouldn't like to answer dogmatically that we don't get some slight increase. We certainly get lymphomas.

DR. MUSTARD: I would like to turn to your fibrosis experiments in which you allowed the rats to inhale dust for a year and then you stopped and looked at the progression of the fibrosis. In those experiments did you carry any rats on for continuous exposure and compare the amount of fibrosis between the two groups?

THE WITNESS: No.

DR. MUSTARD: Has anybody done that?

THE WITNESS: I don't think so. I think most people

THE WITNESS: (contd.) doing inhalation studies have the problem of the limitation of the number of chambers they have and can run. We would have liked to have done something like that, but we haven't done so.

DR. MUSTARD: Okay. The other question in those experiments, was the lifespan of the rats shortened in comparison to rats not exposed to the dust?

THE WITNESS: No. In that we couldn't detect any difference between our exposed populations and our control animals...no obvious difference.

DR. MUSTARD: Did you set it up as a mortality study to see if an effect...

THE WITNESS: Not entirely. We set it up as a fairly simple study. We had the same number of animals in each group. We had groups of controls usually of similar size available. But we weren't examining that point as the major part of the project. We simply wanted to see if we got different numbers in tumors, and only subsequently did we examine the obvious things like the survival time of the animals.

I think we've been very lucky. We've got, so far, a very good animal unit which we've managed to keep very free from infection and can usually take some of our rats up to just under three years, their total lifespan, which I think most rat users would say is very good indeed. Some of those will have been exposed to asbestos.

Now, I think it is surprising if you've got a number of tumors being produced that they don't significantly reduce the overall lifespan figures. I think the answer is that most of them develop in the very old animals, and ten tumors that shorten a rat's life by twenty or thirty days probably don't affect the overall figures in any way that you could show.

DR. MUSTARD: Unless you set it up as a true

DR. MUSTARD: (cont'd.) mortality study, which...

THE WITNESS: That's right, which we did not do.

DR. MUSTARD: Now, in terms of fibrosis, you talked about fibrosis in the lung, in your experiments, but you also talked about injection experiments and mesotheliomas.

In your inhalation experiments did you get many mesotheliomas?

THE WITNESS: The simple answer is no. Neither did we nor Chris Wagner or other people who have done it. They are rare from inhalation, but then after all that appears to be the human situation as well. Whereas we might, in a group of... if we start off with forty-eight rats..say forty of them survive old enough to produce lung cancer, bronchial carcinoma, you might get one, two, perhaps exceptionally, three mesotheliomas...but an average of somewhere around the one. So they occur, but they are rare in inhalation studies.

This is why we do stick to injection studies as well, even though we don't like them very much.

DR. MUSTARD: Now, with the injection studies do you get fibrosis of the pleura?

THE WITNESS: Certainly the first stage of injection will be the production of a very large cellular granuloma, which will fibrose to a large extent.

DR. MUSTARD: And you will get that in all the animals that are injected?

THE WITNESS: You will get that in all the animals that are injected, and only a few will go on to produce tumors sometimes.

DR. MUSTARD: When you get inhalation-induced mesotheliomas, do you also have fibrosis of the pleura?

THE WITNESS: We've got so few mesotheliomas produced by inhalation that that's difficult to answer. What

THE WITNESS: (cont'd.) I can say is that we've got evidence of fibrosis of the pleura on its own in quite a reasonable number of animals, little patches of fibrosis - in animals treated by inhalation.

So fibrosis of the pleura to that extent is not rare. Progression, if that's the right term here, from fibrosis to mesothelioma, is rare.

DR. MUSTARD: In the pleural fibrosis do you have macrophages present? Can you identify them as being part of the pleural scene, and can you identify them as having asbestos fibers associated with them?

THE WITNESS: Where we have done electron microscopy. In light microscopy you can't see any fibers, and we've done limited electron microscopy which has again failed to find fibers.

So there's a little bit of evidence, but we haven't got dust out in the areas of pleural fibrosis, actually in the fibrosis. But I'm not satisfied to make that as a definite statement. It may well be we failed to find it.

DR. MUSTARD: Are the macrophages around?

THE WITNESS: There are a few macrophages, but not many.

DR. MUSTARD: Because one is interested in the role of the macrophage in stimulating the fibrosis.

THE WITNESS: That's right. But it could well be that when we see this fibrosis is when the animal dies of something else and it is relatively slight and it may well be that in the early stages there were macrophages around dust particles and when the animal dies, you can't see them any longer.

DR. MUSTARD: Now I would like to turn to tab thirteen, and it's your summary which is at the very front of the sheet down to level three and level four in Roman numerals,

DR. MUSTARD: (cont'd.) and again pick up John Laskin's point, for the purpose of protection of individuals exposed to asbestos, epidemiological evidence must take priority to that from animal and in vitro experiments.

I realize what you have said to Mr. Laskin's question, and the problem I have is that epidemiological data only shows association. The strength of it is related to the study design and the consistency of the epidemiological evidence, but in the kind of studies that we've had to listen to where they are not forward-designed studies where people have randomized the two groups with precisely-measured exposures that people are going to be given, subject to a tremendous number of variables.

I'm going to apply another interpretation problem where you state that if you go to the animal experiments you have the opportunity to do a controlled, prospective study...you can actually expose the animal in a controlled environment to something that's definable.

It would seem to me that, listening to all the evidence, that you could be trapped in your interpretation of the epidemiological data if one did not take into account what you have told us today, and what I think you've told us today is that fiber size is probably extremely important and that the stability properties of the fiber are also probably extremely important, and that if all exposures were to exactly the same fibers in the human population, the epidemiological data might be different.

In other words, our interpretation of the epidemiological data might be different because we simply do not have that information. We just have very global figures.

So that has to surely be a major reservation on the interpretation of the epidemiological data. Do you see what I'm getting at?

THE WITNESS: Oh, indeed. I'm in a very awkward

THE WITNESS: (cont'd.) position here. It could be that the rat experiments are giving you exactly the right answer for human beings as well, but there is epidemiological evidence, some of it suggesting a position in human beings in certain cases - especially with crocidolite - is rather different.

So you are left with a problem of interpretation, and the statement I made is really a philosophical one. We are saying if you could really trust the epidemiology, it's got to be right because it's with the right species.

DR. MUSTARD: That's true, but I have to have the same precision of measurement, which I can't have.

THE WITNESS: I do agree. I haven't got an easy answer.

DR. MUSTARD: So when you are extracting the ore from the ground and preparing it, you must have a different size, I would presume from the evidence we have listened to, than if you are putting it into cement pipe and grinding it up, which makes the problem very difficult.

So I guess my interpretation is, animal experimental evidence has greater precision. It has to influence one's interpretation of the association, instead of indefinable, and epidemiological evidence.

Is that an uncomfortable statement, to you?

THE WITNESS: No, I would agree with it. You obviously realize that it's a very difficult problem.

DR. MUSTARD: Then the second thing that I find fascinating is the...it's in some of the experimental work you referred to...is this whole question of what happens to the fibers, which obviously is very important. This obviously seems to be very important in a repetitive cycle that might occur to stimulate things, and again, it looks to me as if the animal experimentation is about the only way one can define properties that might be related to that and that you then might go back in and do human

DR. MUSTARD: (cont'd.) post mortem studies to see if you can extract a similar kind of data which would be compatible with the animal evidence.

THE WITNESS: Yes, as long as the animal survives long enough, and we don't have a time factor that spoils everything.

I think this is what we've got to do more work on. The next stage probably is to do some experiments with a slightly longer-lived species and see if we can detect more fiber breakup than is obvious in the rats.

DR. MUSTARD: I think that would be very important. That is certainly Dr. Uffen's point.

One final question on this. You showed in one of your sets of slides mucopolysaccharides...or glycosemated glycens (phonetic) to use the modern biochemical terminology... within the cell associated with a fiber. What is the glycosemated glycen accummulation outside the cell, do you know? Has anybody looked at it? Is there an increased accummulation in some situations?

THE WITNESS: Of course you do get quite a lot of this material in areas of what one might call young, active fibrosis. You find a lot of it in granulomas, so that it wasn't really a surprise to find that it tended to accummulate around partially enclosed fibers for asbestos body formation.

But if you mean is there a quantitative figure as to how much extra there is about, no, I haven't seen one.

DR. MUSTARD: And nobody has looked at whether there is variation in the amount from animal to animal, in relation to the degree of fibrosis?

THE WITNESS: No, certainly not.

DR. MUSTARD: My reason for asking the question, in a totally different cellular system these mucopolysaccharides interefere with the action of mitogens in stimulating cell

DR. MUSTARD: (cont'd.) proliferation, so one of the variables might be that they might modify the degree of fibrosis. So it would be an interesting quantitative thing, but there's no evidence back on that?

THE WITNESS: I don't believe there is any in existence. I certainly don't know of any.

DR. MUSTARD: Okay, thank you.

DR. DUPRE: I have just one question, if you will indulge me, Dr. Davis. You have been very kind to us all day and it is getting on.

The question I have arises out of your tab sixteen, in which you report on the comparison of the effects of animal experiments undertaken with UICC samples, and those undertaken with factory-dust samples. Of course, I noted your conclusion, and to make sure I've got it right, indicated where your chrysotile samples were concerned both the UICC and the factory-dust samples produced similar levels of fibrosis. The factory-dust sample, however, produced less malignancy.

As I read this point, one thing that came to my mind out of our long epidemiology course from last summer was the hypothesis that asbestos becomes more hazardous as you move away from the mine. In other words, each additional step of processing results in a more hazardous kind of fiber dimensions.

Now, at this point I started to ask myself, is your factory-dust sample, as the labelling of it suggests, a sample of dust that was taken from an asbestos manufacturing operation?

THE WITNESS: That's right. It was a textile operation.

DR. DUPRE: Not from a mill related to a mine?

THE WITNESS: No, no. It was a textile factory.

DR. DUPRE: Now, is it possible, for example, that

DR. DUPRE: (cont'd.) a UICC sample, which I gather has more refined asbestos, might be a proxy for the kinds of dust clouds that say insulators or maintenance workers can be exposed to?

THE WITNESS: It's very difficult to answer that. Your basic concept is undoubtedly right - the further away you get from the mine, the more dangerous the dust appears to be.

But I think it would be...

DR. DUPRE: And that would be because there are - if I follow one of your hypotheses correctly - perhaps a higher incidence of long, thin fibers?

THE WITNESS: That's right, because with more and more handling you are tending to break up the bundles and there are more and more long, thin fibers.

Depending on exactly which process you use, you could imagine that some extra handling might actually break down a lot of them, and although I presented hypotheses where this could increase the total number, it need not happen. It could actually reduce the total number.

So when you say is UICC comparable to insulation workers, I just don't know. We haven't looked at dust from insulation processes. I don't know the degree of mechanical breakup that would be involved. It's something that we'll just have to look at on site and examine the figures in detail.

DR. DUPRE: But in any event though, I can take it that your factory dust involved samples taken from textile manufacturers?

THE WITNESS: That's right.

DR. DUPRE: Counsel, any last questions?

MR. LASKIN: I don't believe so, Mr. Chairman.

DR. DUPRE: Dr. Davis, you have been very, very generous with us indeed and you have come a very long way. You

DR. DUPRE: (cont'd.) have been most instructive, and on behalf of all present may I say thank you most warmly.

THE WITNESS: Thank you very much for inviting me.

- - - - - - - - - - - - - - -

THE INQUIRY ADJOURNED

THE FOREGOING WAS PREPARED
FROM THE TAPED RECORDINGS
OF THE COURT PROCEEDINGS

Edwina Macht

EDWINA MACHT